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EPILEPSY AND SURGICAL THERAPY

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TOPICAL HEADINGS

INTRODUCTION

Surgical intervention should be employed in the treatment of epilepsy only when the operator has studied carefully the physiologic

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The words "pathologic" and "neurologic" are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The author would prefer to use the words "pathological," "neurological," etc.

mechanism and the pathologic cause in the individual instance. The surgeon who performs a craniotomy without a carefully considered constructive hypothesis "places himself on a level with the practitioner of the stone age," to use a phrase borrowed from Sir Percy Sargent.[1] There is no excuse today for meddling with a traumatic defect in the skull unless the operator is prepared to deal efficiently and radically with the underlying meningocerebral cicatrix. A craniotomy planned simply to open a puddle of cerebrospinal fluid that fills the dead space over an area of cerebral atrophy or a suboccipital decompression with the avowed purpose of improving the fluid or venous drainage is just as ill advised for an epileptic patient as the removal of a normal colon or adrenal body.[2]

Effective surgical therapy cannot be described without a brief consideration of the pathology of the forms of epilepsy which are susceptible to such treatment. Some understanding of neuropathology should be for a neurosurgeon more than an ornament; it should be the sine qua non of his entrance into the field of epilepsy.

PRELIMINARY STUDY

In order to discover the epileptogenic focus in a case of habitual convulsive seizures careful study must be made of (1) the attack pattern, (2) the neurologic signs, (3) encephalograms and (4) in case operation is undertaken, the responses to direct cortical stimulation.

Pattern of Attack.—The clue to the origin of an attack is its pattern. This should be worked out in every case, from the history if possible; if not, by hospitalization and direct observation. One may employ the hyperpnea method of Foerster to induce an attack or the forced hydration procedure of McQuarrie.[3] That certain features of convulsive patterns have localizing significance has long been recognized (Jackson,[4] Charcot, Holmes[5] Foerster[6]).

1. Sargent, P.: Some Observations on Epilepsy, Brain **44**:312, 1921.

2. An excellent summary of "lost hopes" in the surgical treatment of epilepsy is to be found in a recent lecture by Schürer-Waldheim (Die chirurgische Behandlung der Epilepsie, Wien. med. Wchnschr. **84**:1180 and 1239, 1934).

3. (*a*) Hyperpnea (Foerster's method): The forced breathing is continued for ten minutes and should be energetic enough to produce temporary tetany. This precipitates an attack in less than 50 per cent of the cases. (*b*) If this fails and there are no spontaneous attacks, the hydration test is carried out. The patient is placed under close observation, and fluid intake is forced as high as possible (McQuarrie, I.: Epilepsy in Children, Am. J. Dis. Child. **38**:451 [Sept.] 1929). After forty-eight hours of this forced drinking, hypodermic injections of pitressin are given, six doses at two hour intervals.

4. Jackson, J. Hughlings: Selected Writings of John Hughlings Jackson, edited by James Taylor, London, Hodder & Stoughton, Ltd., 1931.

5. Holmes, G.: Local Epilepsy, Lancet **1**:957 (May 7) 1927.

6. Foerster, O.: Die Pathogenese des epileptischen Krampfanfalles, Deutsche Ztschr. f. Nervenh. **94**:15, 1926.

Too much effort at spatial localization of function in the brain may be open to criticism; yet the evidence from the study of epilepsy indicates that much more discrete localization will be possible in the future than has yet been achieved, although that localization does not mean that the function in question is represented by a spot, a circle or even a gyrus.[6a] It means that an area of gray matter in the brain forms an essential link in a mechanism that may well involve distant tracts and connections.

Those accepted localizing features which I have been able to verify will be reported in this paper and also certain other patterns which have proved of localizing value even though the anatomic explanation may not be obvious (Penfield and Gage[7]). It is evident that an epileptogenic discharge frequently spreads over the surface of the cortex; yet it is evident that it does not spread outward evenly in all directions but rather extends in some specific habitual direction, which seems most often to be toward the motor gyrus. For example, an aura of tingling in the hand may be a prelude to motor convulsive discharge in that member but rarely if ever to visual phenomena which would result from exclusive spread in a posterior direction. Primary loss of consciousness without aura suggests prerolandic localization. With certain exceptions, all auras arise from that part of the hemisphere which lies behind the central sulcus or below the fissure of Sylvius.

Precentral: Primary turning of the head, and usually of the eyes, to the left means discharge in the right hemisphere, and vice versa. Often this turning away from the lesion is transient and is followed by reversal of the direction of gaze, so that the observer may well be misled unless he sees the actual beginning of the epileptic dance.

Primary continued turning of the head to the left, so that the body is turned around, associated with initial loss of consciousness, suggests a lesion of the frontal pole. Turning of the head and eyes to the left without loss of consciousness and without aura probably points to the frontal adversive field (area 6 α β [fig. 1], situated in front of the precentral hand area).

Initial upward turning of the head and eyes may indicate a lesion on the under-surface of one or other frontal lobe. This must be considered a tentative conclusion, not a final one, but I have seen a number of cases which point to that conclusion.

Localized convulsive movements of one extremity or of part of an extremity, which spread gradually by Jacksonian march through other

6a. Brown, G., and Sherrington, C.: On the Instability of a Cortical Point, Proc. Roy. Soc., London, s.B **85**:250, 1912.

7. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, Arch. Neurol. & Psychiat. **30**:709 (Oct.) 1933.

adjacent parts of the body, point to a localization in or near the contralateral precentral gyrus. Whenever the actual convulsive movements begin by rapidly succeeding or simultaneous involvement of all the parts of the body on one side, the discharge has usually begun at a distance from the precentral convolution rather than in it. The disturbance thus has spread to the precentral gyrus over some distance.

The patterns of motor movements which follow discharge within the precentral gyrus are too familiar to require complete description. Movements of the foot and toes come from stimulation within the longitudinal fissure, rarely from the convexity of the hemisphere. Swallowing and salivation result from stimulation above the fissure of Sylvius.

It is a common observation in my experience that well controlled stimulation of the precentral gyrus, probably in area 6 *a* (fig. 1), may give rise only to tingling or numbness in the represented part, without resulting in actual movement, and occasionally the patient may say he had a feeling of wanting to move the part although the observer detects no movement. The same is true of the face and tongue. Distinct areas may be found in the lower part of the precentral cortex stimulation of which will result in a sensation in the side or the center of the tongue, mouth or face.

I have produced vocalization only since using a thyratron stimulator. The tone is monotonous and may be repeated over and over again at will. There are no words. The sound resembles the "epileptic cry" that is habitually heard in the attacks of some patients. The area from which this effect has been produced is closely circumscribed in the precentral gyrus between the hand and face areas.

Before leaving the discussion of the frontal lobe it should be pointed out that the greater portion of this lobe has no local sign in epileptic pattern. Perhaps, like the speech area, which signifies a discharge by silence not by words, the greater portion of the frontal lobe is capable of producing only unconsciousness, not thought, during an attack. Electrical stimulation here is without result, for, with the exception of the cortex a few centimeters anterior to the central fissure and extending about 6 cm. anterior to it in the so-called frontal adversive field, I have never seen electrical stimulation of the frontal lobe produce movement, sensation or an attack.

Postcentral: Tingling and numbness in one part of the body spreading quickly to movement of the part indicate a position in, or in close proximity to, the postcentral gyrus. The lesion under such circumstances is usually found behind the central fissure but occasionally

in front of it.[8] Similar sensation which spreads gradually through the extremities or body on one side with no motor involvement, at least for a time, indicates a lesion placed farther posteriorly in the cortex of the parietal lobe.

Pain may occasionally be complained of as an aura in a contralateral extremity or in the contralateral half of the body as the result of discharge in the convolution posterior to the postcentral gyrus and near the midline (area *5a,* fig. 1), and this can be reproduced by electrical stimulation. But I have never yet observed a case in which a lesion exclusively in the thalamus gave rise to pain as the aura of epileptogenic discharge.

Visual hallucination of light, often colored, in one lateral visual field indicates localization in the posterior portion of the occipital lobe, either lateral or mesial (*17* or *18,* fig. 1). Theoretically one would expect a peripheral hallucination to arise anteriorly on the mesial aspect of the lobe and central hallucination to arise at the occipital pole. Dancing or flickering lights or stars point to the localization of a discharge in the general vicinity of the supramarginal gyrus (*7a* and perhaps *19* and *22,* fig. 1), and this aura may persist after removal of the occipital lobe and in the presence of the resulting complete homonymous hemianopia.

Auditory hallucinations, usually simple sounds described as roaring or rumbling, point to one temporal lobe, and hyperacusis, or increase in the intensity of sounds, has the same significance. Macropsia, or apparent enlargement of objects seen, and micropsia, the reverse, arise from the temporal lobe, probably far posterior. Dizziness is frequently an aura of discharge in one temporal lobe.

The recollection of some situation which may have either visual or auditory aspects also seems to point to one or the other temporal lobe. Such a recollection is likely to bring with it a sense of familiarity, although the patient may have experienced it only in his aura, or his dream state, as Jackson [4] called it. The dream may be as complicated as a visual picture or even as orchestral music. These dream states involve a sort of mental diplopia or double consciousness, as Jackson pointed out, for some hold is kept on present reality. Thus it may be

8. The explanation of this may possibly be the fact that epileptogenic discharge usually begins not in a lesion itself but in the gray matter adjacent to it. The more likely explanation, however, is that some sensory representation exists in the precentral gyrus as well as posterior to the central fissure. Local stimulation of the precentral gyrus frequently gives rise to a sensation of numbness and tingling in the part represented without movement. Furthermore, Dusser de Barenne obtained the same sensory effect by painting the precentral gyrus with strychnine as by painting the postcentral gyrus.

surmised that judgment of the size of objects seen and the intensity of sounds heard must have a neurologic organization in each temporal lobe as well as visual and auditory memory.

General: Epigastric sensation, the commonest of all auras according to Gowers,[9] and the one seen particularly frequently in idiopathic epilepsy, is difficult to localize with certainty. My observations point to a tentative localization adjacent and anterior to the uncus, which would place it in the postero-inferior mesial portion of the frontal lobe near to the supra-optic nuclei and to the ventral nuclei of the tuber, which areas are obviously related to visceral function, according to recent research.

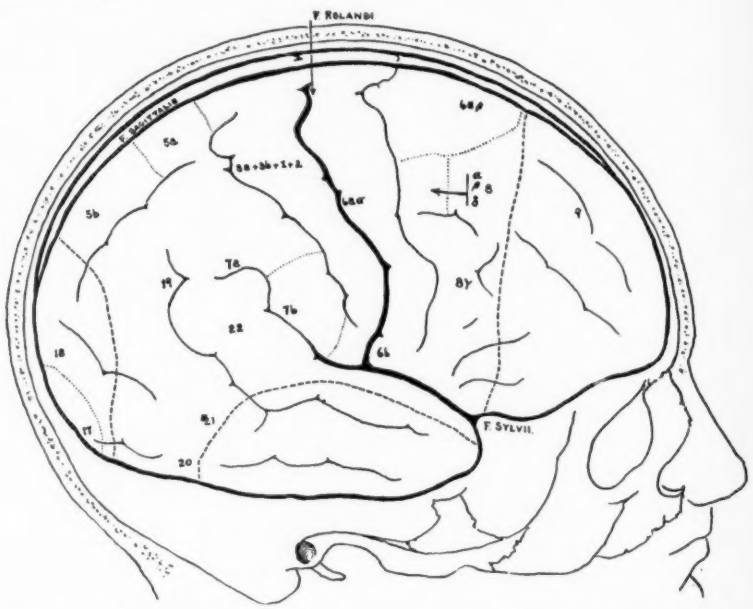

Fig. 1.—Schema of right hemisphere. The numbers refer to the architectonic fields of Brodmann and Vogt.

Petit mal, or slight attacks which involve only a transient loss of consciousness, with little or no disturbance of sensory or motor function, can sometimes not be localized; yet in certain instances there is good evidence that the origin is in one frontal pole, possibly in its under-surface. I have never produced this or olfactory hallucination by electrical stimulation.

Postepileptic automatism depends, no doubt, on properly placed postepileptic ischemia of the brain, as will be pointed out in the section on

9. Gowers, W.: Epilepsy and Other Chronic Convulsive Diseases, London, J. & A. Churchill, Ltd., 1901.

idiopathic epilepsy. What that specific localization may be is as yet undetermined. This ischemia does not necessarily occur in the same site as the preautomatic discharge. At present, therefore, such postconvulsive automatism has no localizing value.

Neurologic Signs.—Nothing need be said here concerning the importance of neurologic signs in the examination of these patients except to point out the frequency with which all signs disappear years after a severe injury to the brain and in spite of the presence of gross cerebral lesions. When the injury to the brain dates from birth or infancy and involves the general region of the central fissure, hemiatrophy of the contralateral side of the body, seen most often in face and thorax, is a frequent finding.

Encephalography.—Encephalographic plates should be interpreted in the light of knowledge of the convulsive pattern of the case in question. The ventricles enlarge locally as the result of destruction in the brain. Traumatic cicatrix produces a pull on the brain, which is indicated by a wandering of the ventricles toward the area (Foerster and Penfield [10]). It must be admitted, however, that atrophy by itself may cause a small amount of displacement of the septum pellucidum toward the lesion as well as a local widening of the ventricle. In the case of meningocerebral cicatrix local superficial cystlike collections of air may be seen on the first or second day after the injection. An expanding lesion, such as an abscess or tumor, naturally produces a decrease in the size of the ipsilateral ventricle and migration of the ventricles away from the focus. To avoid erroneous conclusions each portion of the ventricular system should be completely filled in turn, as in the brow-up and occiput-up positions, and each subdivision of the lateral ventricles should be considered in both the anteroposterior and the lateral view (Torkildsen and Penfield [11]).

Electrical Exploration.—Electrical exploration is available only when a pathologic lesion has been diagnosed and craniotomy undertaken. It is useful to delimit the motor area, so that the surgeon may be oriented accurately for localization of cerebral function. A scar often displaces the cortex a considerable distance, so that the relation of the brain to the skull is no indication of the position of cerebral areas. In case of doubt a seizure may sometimes be produced by stimulation of a questionable area. Attacks are produced in general not by stimulating a lesion but by stimulating the adjacent brain.

10. Foerster, O., and Penfield, W.: Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle, und für die therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930.

11. Torkildsen, A., and Penfield, W.: Ventriculographic Interpretation, Arch. Neurol. & Psychiat. **30**:1011 (Nov.) 1933.

If the seizure resembles in pattern the attacks from which the patient habitually suffers, the conclusion may be drawn that the firing point for the attacks has been found. But the operator must not believe that he has found the focus when stimulation of the motor cortex produces the gross convulsive part of the seizure without the preliminary train of events which would indicate the true origin of the patient's habitual seizures far from the motor gyrus.

A galvanic current, not over 8 milliamperes in intensity, may be used to outline motor and sensory areas. A faradic coil may then be used to produce a seizure, the strength of the current being just great enough to produce a motor twitch in the exposed temporal muscle. But great care must be taken, as paralysis may be produced by too enthusiastic stimulation with either of these currents. I have found recently that a thyratron stimulator is a much better instrument for all stimulation and have used it set at a frequency of about 56, which Dusser de Barenne [12] has found most effective experimentally. This gives much more circumscribed responses than any previous form of current used and affords greater safety. Each response should be recorded and a marker placed on the brain (fig. 2). Either unipolar or bipolar electrodes may be used. I prefer a platinum electrode in a glass holder. If unipolar stimulation is selected, the indifferent electrode, a copper plate, may be clamped on the exposed temporal muscle; electrodes and wires must be autoclaved.

If accurate conclusions are to be obtained from electrical exploration, the operator must be in complete sympathy with the patient and must verify every observation without overtiring him, and the anesthetist, relieved of any responsibility for anesthesia, must be a trained observer. No sedative should be used until the observations are finished.

IDIOPATHIC (ESSENTIAL) EPILEPSY

Under this heading are grouped those cases of epilepsy in which no primary cause can be demonstrated and in which no gross neurologic abnormality can be detected. Only after careful study should a case be relegated to this class.

For the most part idiopathic epilepsy lies outside the field of neurosurgery, but I have carried out exploratory craniotomy in a number of instances because of suspicion of a removable focal lesion or for some other reason and have thus had the opportunity of studying the cerebral cortex in patients with this condition during and after seizures.

Pathologic Physiology.—The pathologic physiology of epilepsy is best studied on the operating table, for although a gross lesion may be examined post mortem, the physiologic mechanism can be studied only

12. Personal communication to the author.

during life. However much the gross appearance of the brain may vary from one patient to another, there is uniformity in the phenomena witnessed during a seizure.

When a large area of cerebral cortex is exposed at operation under local anesthesia and without the use of any sedative, a typical attack can usually be induced by minimal electrical stimulation at what may be called the trigger zone. To be called typical, the attack must be judged identical with the patient's habitual attacks both by the patient himself and by an observer.

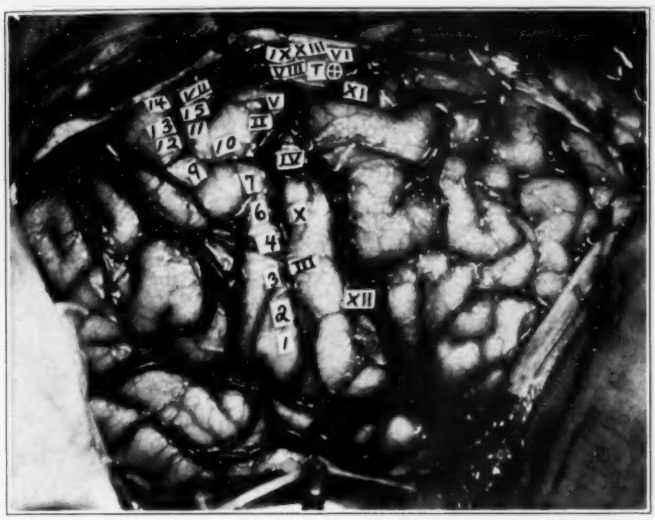

Fig. 2 (F. S.).—The numbers on the surface of the right hemisphere indicate definite responses to thyratron stimulation: *4*, sensation in the tip of the tongue "like little points"; *6*, sensation in the upper teeth, more on the left; *7*, sensation on the outside of the mouth, left, repeated once later; *9*, sensation in the left thumb and index finger, "like shaking of nerves," no movement observed; *10*, closure of the thumb and index finger; *14*, sensation in all the fingers, most intense in the little finger; *12*, sensation in the middle finger and index finger; *15*, slight twitching of the little and ring fingers; *II*, slight closure of the hand and sensation in the thumb and fingers; *III*, twitching of the left angle of the mouth "like the mouth does in an attack"; *IV*, the patient stated that he wanted to pull the mouth to the left side; no movement was seen; *VIII*, "nerves shook all over. Wanted to pull me to left." "Looks like an attack." Patient agitated; *X*, patient said "I am going to have an attack." For six seconds the eyes were turned to the left and upward in rhythmic, nystagmoid jerks. No other convulsive movements were seen. When the area indicated by a cross in a white circle was stimulated a convulsive seizure occurred as follows: (*a*) the patient felt the attack coming on; (*b*) the eyes were turned up and to the left; (*c*) the pulse disappeared at the wrist and in the arteries on the cortex; (*d*) clonic movement of both arms appeared, more marked on the left; (*e*) the pulse returned; (*f*) the eyes turned back to the other side; (*g*) midline twitching of the mouth occurred for a short time. Then the patient said "the attack is over." An atrophic epileptogenic focus was excised from the frontal adversive field about the area marked by the cross.

At the initiation of an attack I have never observed the widespread shrinking of the brain reported by Foerster,[6] and there is at that time no sudden diffuse anemia or obvious constriction of the vessels in the pia.[13] The initial phenomenon evident in the brain during an attack is the cessation of pulsation in the pial arteries.[14] This is usually widespread over the hemisphere even though the seizure may involve only one part of the body in a local motor or sensory fit. Only occasionally the cessation of cortical pulsation has seemed to be restricted to a local area of the brain. If there is respiratory difficulty, the veins become overfull, the venous pressure becomes high and the brain may then bulge—all as secondary phenomena. If there is no respiratory difficulty the brain does not bulge, there is no venous engorgement, the veins may collapse and the arteries become gradually blue. At the close of the seizure the arteries begin to pulsate, and soon they do so more vigorously than before the seizure.

Toward the end of the attack, or more often after the cessation of the attack, there may occur extraordinary alterations in the vascularization of the cerebral cortex. Most often there appears an area of focal anemia or blanching of the cortex (fig. 3). There may appear single or multiple constrictions of large pial arteries obviously capable of arresting the flow of blood through the vessels (*A 1* inset, fig. 3). On the other hand, there may appear as a sequel to an attack marked flushing of several gyri, so much so that the veins themselves take on an arterial hue. These convulsive sequelae occur for the most part in those areas of the brain which had been involved in the production of the epileptic manifestations.

Such vascular sequelae appear only in habitual epilepsy. Even after similar electrical stimulation the cortex of patients who are not subject to epileptic seizures presents no such phenomena. Dr. Lyle Gage and Dr. Joseph Evans, working in our laboratory, have repeatedly attempted to reproduce these sequelae in animals, but even after epileptiform seizures were precipitated in monkeys and in cats by convulsant drugs or by electrical stimulation, no such vascular phenomena were

13. Sargent[1] quoted Cushing to the effect that electrical stimulation causes blanching. I have watched for this both at the operating table and experimentally but have not seen it except at times in an area not greater than from 1 to 2 mm.

14. Etienne (Le rôle des spasmes vasculaires, des troubles vago-sympathetiques et des troubles endocriniens dans la pathogénie de l'épilepsie, Rev. méd. d. l'est **61**:249 [April 1] 1933) reported disappearance of the pulse in the arm with each succeeding seizure during status, although the heart could be heard faintly. I have frequently noted disappearance of the radial pulse with the onset of an attack.[16]

seen. Furthermore, experimental stimulation of sympathetic or parasympathetic nerves to the brain will not produce such changes experimentally.[15]

These vascular phenomena (Penfield[16]) are a great deal more pronounced in idiopathic, or so-called essential, epilepsy than in conditions in which an obvious gross lesion exists. It is probable that the cerebral vessels of the patient with idiopathic epilepsy respond more

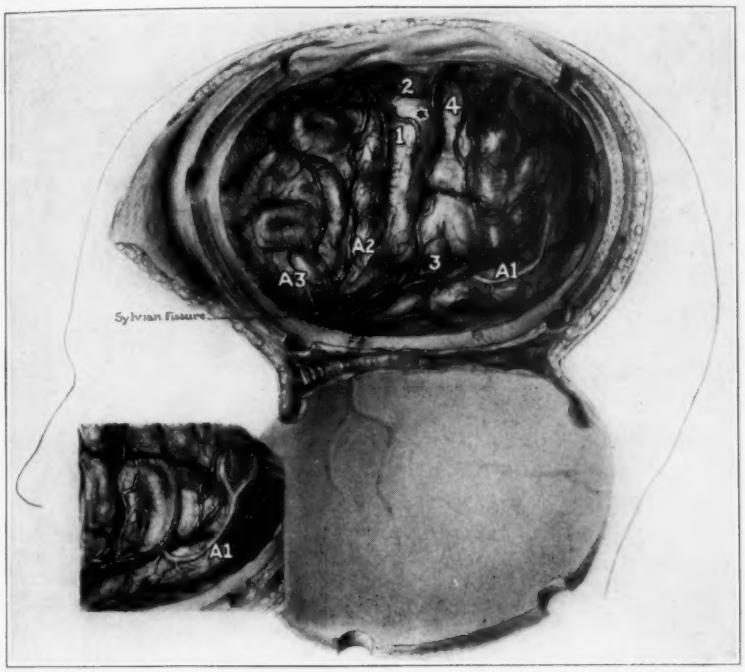

Fig. 3 (M. B.).—The patient had essential epilepsy with no focal lesion. A unilateral convulsive seizure was produced by stimulation of the precentral gyrus at the point indicated by the star. During the attack visible pulsation disappeared in the cerebral arteries; the veins became darker, and some of them became almost black. With cessation of convulsive movements, the arteries began to pulsate violently. Toward the close of the attack great pallor developed in the precentral and postcentral gyri as indicated. After the attack was over, constriction developed in artery *A 1*, as shown in the inset. A second seizure followed spontaneously, which was followed by or associated with the second area of blanching indicated in the inset. When ether was given to stop continuance of the seizures the brain became diffusely suffused.

Reproduced from a previous article.[16]

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15. For a description of the parasympathetic innervation of the cerebral vessels see Cobb and Finesinger (Vagal Pathway of Vasodilator Impulses, Arch. Neurol. & Psychiat. **28**:1243 [Dec.] 1932), also Chorobski and Penfield.[22]

16. Penfield, W.: The Evidence for a Cerebral Vascular Mechanism in Epilepsy, Ann. Int. Med. **7**:303, 1933.

actively than those of the normal person to external stimuli, whether these stimuli are substances circulating in the blood stream or afferent nervous impulses affecting the brain.

Epileptic persons in general and persons with idiopathic epilepsy in particular have thus a common organic abnormality. This common factor is cerebral vasolability, if one may venture to give it a name.

There is no final proof that vasomotor phenomena actually cause the attack. We have proof only that such phenomena are accompaniments and sequelae, as surmised by Wilson.[17] However, it seems obvious that postconvulsive paralysis is not an evidence of fatigue, not a manifestation of active inhibition, but the direct result of the subsequent cerebral anemia which follows the attack and which most often affects the cerebral storm center, but which may appear in the brain at some little distance. This explains the fact that paralysis and convulsion do not always correspond, as pointed out by Gowers,[9] and, further that a very slight motor seizure may be followed by severe paralysis.

The anatomic features of the cerebral vessels are as follows: All the vessels of the brain down to 40 microns in diameter have been demonstrated to bear vascular nerves and occasional endings which resemble motor end-plates (Stöhr,[18] Hassin,[19] and Penfield[20]). In monkeys, complete cervicothoracic sympathectomy results in the appearance of degenerating nerve fibers on the pial arteries as seen by impregnation with silver[21] during the first week following operation. But after such complete removal and after section of the greater superficial petrosal nerves which carry the parasympathetic nerve fibers to the blood vessels of the brain, there will still remain perivascular nerves in plexuses on these vessels (Chorobski and Penfield[22]). These remaining vascular nerves may arise from ganglion cells on the largest

17. Wilson, S. A. Kinnier: Modern Problems in Neurology, New York, William Wood & Company, 1929.

18. Stöhr, P., Jr.: Mikroskopische Anatomie vegetativen Nervensystems, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, p. 143.

19. Hassin, G. B.: The Nerve Supply of the Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. **9**:437, 1930.

20. Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**:30 (Jan.) 1932.

21. For a modification of the Gros-Bielschowsky technic, which we have found most useful for staining vascular nerves on intracerebral arteries as well as pial arteries, see Penfield (A Technique for Demonstrating the Perivascular Nerves of the Pia Mater and Central Nervous System, Am. J. Path. **11**:1007 [Nov.] 1935).

22. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

pial arteries, of which there are occasionally a few, or they may be derived directly from the brain by some route not yet discovered. Stavraky,[23] working in the laboratory of the Montreal Neurological Institute, has demonstrated that the cerebral vessels may be caused to constrict or to dilate by stimulation of different areas of the hypothalamus. Central control of these vessels thus exists, although the efferent pathway from the hypothalamus to the cerebral vessel is unknown.

Results of Sympathetic Ganglionectomy.—The foregoing description of the pathologic physiology of essential epilepsy might seem to suggest removal of the sympathetic nerves, which accompany the cervical arteries to the brain, as a rational therapeutic attack. But, alas, such is not the case. Sympathectomy has been given a sufficiently long trial and has proved a disappointment (Alexander, Jonnesco et al.). Foerster[6] expressed the opinion that it may make patients worse.

In a few instances of well controlled epilepsy, in which there was obvious abnormality of the autonomic nervous system in association with the epilepsy, I have carried out complete cervicothoracic sympathetic ganglionectomy and have added to it periarterial sympathectomy of both internal carotid arteries and of both vertebral arteries.[24] In only 1 instance did the procedure bring undoubted improvement.

Case 1.—R. G., a man aged 45, had generalized seizures for thirty years. Encephalography showed no focal lesion but a diffuse enlargement of the ventricles. Operation was performed six years before the time of writing—bilateral superior and inferior cervicothoracic sympathectomy, with decortication of both carotid arteries and of both vertebral arteries.

No improvement was noted in the number of attacks or in his retarded mental state.

Case 2.—M. B., a boy aged 15 years, had so-called encephalitis with transient paralysis of the right arm at the age of 9 years. Jacksonian seizures in the right arm began at 11 years. Exploratory craniotomy at 12 years showed the remarkable areas of anemia seen in figure 3.

The second operation was a superior and inferior cervicothoracic sympathetic ganglionectomy on the left side. No improvement was noted, and the attacks were unchanged. At the time of writing gradual deterioration is continuing.

Case 3.—A. M., a man aged 30, had suffered attacks since he was 9 years of age. There was a history of severe previous injury to the head. The attacks apparently arose in the left hemisphere. When the patient was 27, I carried out exploratory craniotomy of the left hemisphere. An area of marked cortical

23. Stavraky, G. W.: Response of Cerebral Blood Vessels to Electric Stimulation of the Thalamus and Hypothalamic Regions, Arch. Neurol. & Psychiat. **35**:1002 (May) 1936.

24. The procedure was carried out through four incisions in two stages, the anterior approach being used in each case. It is impossible to reach the vertebral artery or the ganglion usually found on it through the posterior incision of Adson.

atrophy was seen but was not removed. Marked spasm of the cerebral arteries followed the induced seizures. No improvement followed this exploration.

The second operation was done when the patient was 30, two years before the time of writing. Complete bilateral superior and inferior cervicothoracic sympathectomy was carried out. The severe attacks disappeared for two years, but minor seizures continued. Little real improvement followed.

CASE 4.—H. H., a boy aged 19, had generalized seizures from childhood. The seizures were associated with marked pallor of the face. Encephalography showed a grossly normal brain.

Bilateral superior and inferior cervicothoracic sympathetic ganglionectomy and decortication of the carotid and vertebral arteries were done in two stages.

After sympathectomy on the right side the deep reflexes became a little more active on the left, so that a distinct difference existed in the activity of these reflexes on the two sides. He also had several attacks at that time, which were one-sided, beginning on the right. This was in contradistinction to the generalized seizures which he had had before the unilateral sympathectomy.

After the operation on the second side was done and the bilateral sympathectomy was completed, he was free from attacks for several months. The attacks have returned at the time of writing in two forms: small seizures, almost myoclonic, and petit mal syncopes. There have been no further major seizures in the four years since operation. This patient showed real improvement in his mental condition as well as cessation of major seizures. The reflex change that followed sympathectomy on one side probably indicated some alteration in the nutrition of the corresponding hemisphere.

These patients had all shown some vascular instability either at the operating table or in their seizures; yet complete removal of all sympathetic nerves entering the skull did not make epilepsy impossible. One patient may have become worse after operation; 2 were little changed and 1 was definitely better, perhaps as the result of some alteration of cerebral nutrition.

Furthermore, Gage (thesis accepted for M.S. degree McGill University) found that although in monkeys complete cervicothoracic sympathectomy served to raise the convulsant threshold, attacks could still be produced by camphor. In one monkey removal of sympathetic trunks and section of the parasympathetic greater superficial petrosal nerve influenced the convulsant threshold very little.

It is possible, therefore, to draw the following conclusions in regard to sympathectomy: Typical seizures are still possible in persons with habitual epilepsy (and epileptiform convulsions can still be induced, although with somewhat greater difficulty, in experimental animals) after complete cervicothoracic sympathetic ganglionectomy. That such an operation may alter the functional activity of the brain of the epileptic person, perhaps by means of improved circulation, and may greatly decrease the number and severity of seizures is indicated by case 4. But sympathectomy, however complete, does not make seizures impossible and is hardly justifiable as a treatment for epilepsy except

in the presence of unusual evidence of abnormality of the sympathetic nervous system. In such instances it may be looked on as an aid but not as a cure.

Results of Removal of the Carotid Body and Denervation of the Carotid Sinus.—Lauwers [25] reported that between 1927 and 1930 he carried out on 40 patients with epilepsy an operation which he described as an outgrowth of the periarterial maneuver of Leriche. The operation was called extirpation of one carotid body. The removed tissue did not always contain chromaffin alveoli, but in every instance nerve fibers and ganglion cells were included. He reported 10 cases as instances of cure; in 12 the condition was improved; 21 operations were failures, but none made the condition worse. His conclusion was that the best results were obtained in instances in which no lesion of the nervous system existed and that the procedure should be limited to cases in which examination of the vestibular canals demonstrated great daily variability in caloric excitability and especially those in which there was dissociation between the caloric and rotatory vestibular reflexes. It is difficult to follow the relation between these reflexes and the indications for operation on epileptic persons. Further report from Lauwers concerning these patients may make possible a practical conclusion as to the value and indications of the procedure.

The theoretical justification of procedures such as that just cited may be discussed briefly. Afferent fibers pass to the medulla oblongata from the carotid sinus through the glossopharyngeal and perhaps through the hypoglossal nerve in man, stimulation of which produces a fall of blood pressure by means of peripheral dilatation and slowing of the heart rate.[26] In 1878 François-Franck found that very strong experimental stimulation of the central end of the cardio-aortic nerve produces convulsive attacks. This was confirmed by later workers.

Danielopolu [27] even suggested section of both the carotid nerves, extensive sympathectomy and section of the right vagus nerve below the recurrent laryngeal nerve as treatment for epilepsy. It is difficult to understand the rationale of such a procedure, and Heymans and Bouckaert [28] warned against it in no uncertain terms; they stated that

25. Lauwers, M.: Le traitement chirurgical dans les épilepsies, Rev. neurol. **39**:1377, 1932.

26. An excellent analysis of the carotid sinus reflex is to be found in a recent publication by Weiss and Baker (The Carotid Sinus in Health and Disease, Medicine **12**:297, 1933).

27. Danielopolu, D.: Sur la pathogénie de l'épilepsie et sur son traitement chirurgical, Presse méd. **41**:170, 1933.

28. Heymans, C., and Bouckaert, J.: Au sujet de l'influence des zones vasosensibles réflexogènes de l'aorte et des sinus carotidiens sur l'excitabilité corticale motrice, Presse méd. **41**:729, 1933.

grave pathologic lesions develop in animals after section of the so-called vasosensory reflexogenic nerves.

Czermak in 1866 reported dizziness from pressure on his own sinus caroticus, and Roskam reported the case of a patient who could be plunged into syncope and violent convulsion by slight pressure on the carotid sinus of one side. Gibbs, Lennox and Gibbs [29] suggested that the convulsion which Leonard Hill produced in himself when he compressed his own carotid sinus with such fortitude was in reality the result of a carotid sinus reflex. Weiss and Baker [26] observed 15 patients who had a hyperactive carotid sinus reflex on one or both sides. Thirteen of these patients complained of spontaneous dizziness and fainting attacks. Six of the 15 patients had an aneurysmal dilatation of one or both carotid sinuses. In 3 instances a small tumor impinged on the sinus, and in the remaining 6 no gross abnormality was found. They found that pressure on one or both of the carotid sinuses in these 13 patients produced dizziness and fainting together with convulsive seizures. They found further that fainting and convulsions occurred only if the subject was erect and not in the horizontal posture and provided the change was brought about suddenly.

Whatever the nature of the carotid sinus reflex may be, cerebral ischemia evidently plays an indispensable rôle when its activity results in convulsion. Furthermore, there is no tendency among persons with epilepsy to hyperactivity of the carotid sinus, according to Lennox,[30] who was unable to produce seizures in 150 epileptic persons tested by stimulation of the sinus. Weiss and Baker concluded that the reflex plays no rôle of any importance in the production of idiopathic epilepsy and that denervation of the sinus should be considered only when specific abnormal hyperactivity of the carotid sinus exists. Marinesco and Kreindler [31] reported that the sensitivity of the carotid sinus is decreased in essential epilepsy, and they therefore advised strongly against any further decrease in this activity by surgical intervention. Ask-Upmark,[32] after an exhaustive analysis of the relation between the carotid sinus and the cerebral circulation, advised against the operation of Lauwers.

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29. Gibbs, F. A.; Lennox, W., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257 (Aug.) 1934.

30. Lennox, W.: Personal communication, cited by Weiss and Baker.[26]

31. Marinesco, G., and Kreindler, A.: Des réflexes du sinus carotidien en pathologie nerveuse, J. de physiol. et de path. gén. **29**:77, 1931; quoted by Ask-Upmark.[32]

32. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation: Anatomical, Experimental, and Clinical Investigation, Including Some Observations on the Rete Mirabile Caroticum, Acta psychiat. et neurol., supp. 6, 1935, p. 1.

Results of Subtemporal Decompression.—This maneuver was recommended early by Kocher and has been tried empirically by many surgeons. In an attempt to rationalize the procedure it may be pointed out that Lennox (quoted by Cobb [33]) measured the cerebrospinal fluid pressure in 400 persons with epilepsy. He found it normal in about 71 per cent, low in 8 per cent and high (from 200 to 250 mm. of water, with the patient horizontal) in 17 per cent. Elsberg and Pike [34] showed that a rise in the cerebrospinal fluid pressure increased the liability of animals to experimental seizures.

In a considerable number of those instances of idiopathic epilepsy in which I have carried out an osteoplastic craniotomy for one reason or another, the dura has seemed to be under increased pressure before it was opened, even though the operation was carried out without the use of a general anesthetic or of a sedative. In such instances a subtemporal decompression was made when the bone flap was replaced.

The results were as follows: In 14 instances subtemporal decompression was carried out after an osteoplastic exploratory craniotomy which gave negative results.[35] In 6 of these it was specifically noted on the operative record that the pressure seemed high before the dura was opened, and it is likely that the same was true in most of the remaining instances. One patient expressed the belief that the operation made him worse. Two patients professed to have been improved for from one and one-half and one and one-fourth years up to the time of writing, and only 1 has been free from attacks for one and one-half years up to the time of writing. To compare with these, 10 patients had similar exploration with negative results but the craniotomy wound was closed without decompression. The results were all failures, with the exception that 1 patient had no further seizures for a period of five years up to the time of writing and 1 patient was improved (two seizures in two and one-half years).

In each of the instances of cessation of attack no objective lesion of the brain was found, and it seems likely that both may be examples of the spontaneous arrest which sometimes occurs in essential epilepsy but rarely, if ever, with gross lesion of the brain.

In conclusion, the results of subtemporal decompression do not justify the procedure in cases of essential epilepsy, and this operation

33. Cobb, S.: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245 (May) 1932.

34. Elsberg, C., and Pike, F.: Studies on Epilepsy: Influence of General Increase or Diminution of Intracranial Pressure upon the Susceptibility of Animals to Convulsive Seizures, Am. J. Physiol. **76**:593, 1926.

35. By negative results here is meant the finding of a normal-appearing brain or diffuse cortical atrophy.

should not be undertaken unless it is as a final incident in an exploration during which the surgeon has failed to find a removable lesion. The real value of decompression appears in those rather rare instances of epilepsy secondary to subdural exudation of fluid which will be described.

Results of Spinal Insufflation of Oxygen.—It is a common finding among those who have carried out encephalography on a large number of epileptic patients that the procedure is occasionally followed by improvement in the patient's condition and cessation of seizures for varying periods up to a year or two. Friedmann and Scheinker[36] urged that encephalography sometimes constitutes a life-saving procedure in cases of status epilepticus, a claim that has also been made for repeated lumbar puncture.

An analysis of the effect of encephalography in our clinic has been made by Dr. J. N. Petersen. He found that of 123 persons with epilepsy followed, who had no other change in regimen, 10 per cent had remained attack-free up to the time of analysis, and another 10 per cent stated that they considered their condition improved. On more careful analysis there were 96 patients who were followed for more than a year, and 5 of these had remained attack-free for an average of two and eight-tenths years. This gratifying result occurred only in young patients, under 16 years of age, with attacks of not over four years' duration. There were 21 such patients, which gives relief from attacks for that length of time in 23.8 per cent of that group. This might suggest that for such patients spinal insufflation is worthy of trial as a purely therapeutic procedure.

EPILEPTIFORM SEIZURES SECONDARY TO SUBDURAL EXUDATION

Beneath the dura there is normally a real and not a potential space. This space contains a thin layer of fluid, which has a yellow tinge, in contradistinction to the colorless cerebrospinal fluid (Penfield[37]). Hematoma within the subdural space is coming to be recognized by the medical profession, but exudation in this space producing an increase in the amount of subdural fluid is a distinct pathologic entity not generally recognized.[38] Owing, no doubt, to the high protein content of the fluid, an abnormal increase in its amount may continue in this space for long periods without absorption taking place, just as a hema-

36. Freidmann, R., and Scheinker, J.: Ueber therapeutische Erfahrungen mit der lumbalen Lufteinblasung bei epileptischen Anfällen, Deutsche Ztschr. f. Nervenh. **133**:35, 1933.

37. Penfield, W.: Cranial Subdural Space, Anat. Rec. **28**:173, 1924.

38. The diagnosis of Quincke's meningitis has been made in some of these cases.

toma may be present in that space for months or even years without absorption. The following cases will indicate the relation which such an effusion may have to chronic recurring epileptiform seizures.

These cases represent the only instances in which a diagnosis of subdural exudation has been made as a primary cause of epileptiform seizures. The results and the similarity of the pathologic findings make me consider them as a tentative group despite the small number of cases.

CASE 1.—A. M., aged 28, was referred by Dr. A. H. Gordon of Montreal, Canada. Three years previously he had an attack of acute mastoiditis, and a mastoidectomy was done on the right side. In three or four weeks he returned to his classes at the University of British Columbia. Two months after operation there developed unexplained diplopia and chronic headache. Seven lumbar punctures were done at that time. The diplopia gradually disappeared as well as the headache. About a year after the mastoidectomy was performed, he began to have major epileptic seizures. The attacks were ushered in by a dreamy feeling, and he apparently turned to the left at the onset of the convulsive movements.

He was admitted to the Royal Victoria Hospital, where encephalograms showed only that there were unusual mottling and increased complexity of the pattern of subarachnoid air. Trepanation was carried out 4 cm. above and 4 cm. behind the external auditory meatus on each side. Fluid, which was definitely yellow, escaped from beneath the dura on each side.

In the five years since operation he has had only three attacks, all of them at the time of an intercurrent illness. He has given up phenobarbital and is working full time.

CASE 2.—P. W., aged 41, who was referred by Dr. Gorham Brigham and Dr. Stanley Cobb, of Boston, and by Dr. Rawle Geyelin, of New York, had had epileptiform seizures, apparently arising in one temporal lobe, periodically for five years. Between the ages of 5 and 36 she had a foul-smelling discharge from the left ear. Roentgenograms showed sclerosis of the left mastoid bone.

Preoperatively a tentative diagnosis of extradural abscess was made. A subtemporal decompression on the left side was carried out. An unusually large amount of fluid was found beneath the dura. The surface of the brain was definitely a little yellow. No attack was produced by stimulation. Unusual veins were found on the crest of the petrous bone. A second decompression was carried out at once under the right temporal muscle; a similar increase in subdural fluid and yellowing of the pia-arachnoid were found here. There was moderate atrophy of the cortical convolutions on both sides.

During the five years since operation there have been no further epileptiform seizures, and the patient has resumed her normal life. Nothing further has been done to the mastoid.

CASE 3.—T. A., aged 29, who was referred by Dr. C. A. Peters, of Montreal, Canada, had had major and minor epileptic seizures for fifteen years and chronic otitis media for about the same length of time. A radical operation on the mastoid had been done three years before the craniotomy. Encephalography showed no evidence of a focal lesion, but the subarachnoid space was outlined by air in a diffuse and unusually spotty manner.

A tentative diagnosis was made of chronic increase in subdural fluid secondary to the chronic mastoiditis. Bilateral subtemporal craniotomy was carried out. The dura on the first side opened seemed tense. When it was incised, there was a gush of fluid from the subdural space, without any evidence of injury of the arachnoidea. On the second side there was a continued flow of fluid from beneath the dura. The arachnoidea had obviously not been opened, as the intergyral sulci stood out filled with fluid until the arachnoidea was incised. The dura was left open; the temporal muscle and the scalp were closed.

The patient was free from attacks for six months after the operation, but they have returned with almost the old frequency. The preoperative duration of the seizures was perhaps much too great for a good result.

It seems probable that after the primary process in the mastoid (or paranasal sinus?) subsides, the increased fluid continues in the subdural space and that evacuation from this space allowing drainage to continue through the opened dura into the temporal muscle is adequate to rectify the condition.

EPILEPSY ASSOCIATED WITH INJURY AT BIRTH AND WITH CONGENITAL ABNORMALITY OF THE BRAIN

There is in general no surgical treatment of true congenital defect of the brain. On the other hand, scars caused by injury to the brain from birth trauma may be susceptible of successful excision in instances in which mental activity is normal and the attacks clearly arise from the margin of the remaining scar (compare cases 5 and 8, Foerster and Penfield[10]). This question will be discussed later under the heading cerebral cicatrix.

Hemiatrophy of the face, thorax, arm or leg, even in the absence of paralysis, is frequently encountered in patients in whom epilepsy is associated with a lesion in the vicinity of the contralateral fissure of Rolando, provided the lesion dates from infancy. Such inequality of growth should not be taken as evidence that the lesion is a congenital one; it indicates merely that it has been present from infancy. It may therefore be due to injury at birth or to prenatal or to postnatal injury, which will be discussed later.

EPILEPTIFORM SEIZURES SECONDARY TO INTRACRANIAL TUMORS

Among patients whose convulsive seizures begin in adult life, tumor is perhaps the most frequent single cause of the seizures. From the other point of view, Sargent[1] reported that a series of 270 patients with supratentorial tumor, exclusive of pituitary neoplasm, 30 per cent suffered from epileptiform seizures, and Parker[39] found that of 212 cases at the Mayo Clinic similarly chosen, major seizures were recorded

39. Parker, H. L.: Epileptiform Convulsions: Incidence of Attacks in Cases of Intracranial Tumor, Arch. Neurol. & Psychiat. **23**:1032 (May) 1930.

in 31.6 per cent. Parker excluded from his figures attacks in which consciousness was not lost and seizures of the petit mal variety.

Analysis [40] of the cases of supratentorial tumor in which operation was performed in our clinic during a given period by Dr. Cone, Dr. Elvidge and myself, including all forms of true epileptiform fits, shows a considerably higher incidence of seizures. Only the commoner forms of tumor will be mentioned here.

TABLE 1.—*Incidence of Epileptiform Seizures*

Cerebral Tumors	Number of Patients	Number with Fits	Percentage with Fits
Glioblastoma multiforme	32	14	44
Oligodendroglioma	7	6	86
Astrocytoma	31	26	84
Meningeal fibroblastoma	31	22	71

In comparison of the rapidly growing, infiltrating glioblastoma with the other three more slowly growing neoplasms, it is evident that the higher incidence is found in the latter. No doubt if patients with glioblastoma lived longer, more of them would have convulsive seizures. The higher incidence of seizures associated with tumor in our clinic than in other clinics is difficult to explain. It may be because of our especial interest in epilepsy, which sometimes brings in patients who are supposed to have ordinary epilepsy, but who prove to have tumor of the brain (fig. 4), and it may further be due to the fact that because of this interest greater attention is paid to recording convulsive phenomena on the history chart.

Of the 26 patients with astrocytoma associated with epileptiform seizures, 7 are now dead and 4 others could not be followed, which leaves 15. Only 2 of these 15 (13 per cent) had been completely relieved of convulsions when this paper was written, these 2 having been free from attacks for thirty-two and sixty-six months, respectively. The other 13 patients have continued to have seizures at intervals, although nearly all have had them less frequently than before operation.

Of the 21 patients with meningeal fibroblastoma, 12 can be followed at the present time, and it may be assumed that the removal was complete in all of them. Of these, 5, or 42 per cent, have been cured of their seizures by operation for periods varying between sixteen months and six years up to the time of writing, while 7 patients, or 58 per cent, have continued to have seizures, although less frequently than before operation.

40. For a complete analysis of the epileptiform seizures associated with tumor in our clinic I have to thank Dr. I. Tarlov. Subtentorial and pituitary tumors are excluded.

EPILEPTIFORM SEIZURES ASSOCIATED WITH MENINGOCEREBRAL CICATRIX, CEREBRAL CICATRIX AND CEREBRAL ATROPHY

There is a striking difference in the incidence of epilepsy after injury to the head with penetration of the dura and injury to the head without such penetration. Wagstaffe [41] reported that 1.6 per cent of patients suffering severe head injuries from war wounds became epileptic when the dura had not been penetrated and 18.7 per cent among those in whom the dura had been penetrated; penetration of the dura thus renders subsequent epileptiform seizures ten times more likely. Schürer-Waldheim [2] estimated that epilepsy developed in 25 per cent of the patients with war wounds involving the brain. Steinthal and

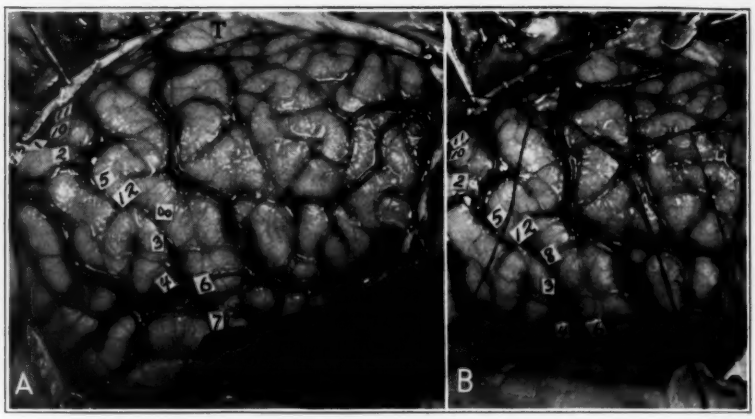

Fig. 4 (H. M.).—Right osteoplastic craniotomy and removal of an astrocytoma were performed. The patient, aged 32, had suffered from epileptiform seizures for five years. There were no headaches. Neurologic and encephalographic examination gave negative results. The pattern of attacks suggested right frontal adversive field, turning of the head and eyes to the left at the onset being quickly followed by generalized seizure.

In *A* the stimulation numbers lie on either side of the fissure of Rolando. The convolution marked "*T*" contained a neoplasm at a depth of 3 cm. from the surface. In *B* the extent of excision is indicated by the position of silk threads which cut out the tumor when tied. Complete removal was effected up to the precentral gyrus.

Nagel [42] reported that in 28.9 per cent of the patients suffering severe injury to the brain frank epilepsy developed, while in 35.5 per cent there were lesser epileptiform manifestations. Finally, Stern's

41. Wagstaffe, W.: The Incidence of Traumatic Epilepsy After Gunshot Wound of the Head, Lancet **2**:861 (Oct. 27) 1928.

42. Steinthal, K., and Nagel, H.: Die Leistungsfähigkeit im bürgerlichen Beruf nach Hirnschüssen mit besonderer Berücksichtigung der traumatischen Epilepsie, Beitr. z. klin. Chir. **137**:361, 1926.

analysis indicated that from 20 to 50 per cent of patients with open injuries to the brain became subject to fits, as against from 2 to 4 per cent of those with what he called "closed injuries" (quoted by Schou [43]).

Thus it is evident that posttraumatic epileptiform seizures result not so much from the severity of the blow to the head as from the penetration of the dura, which must produce a meningocerebral cicatrix. The figures cited indicate that some form of epilepsy develops in nearly as many patients in association with meningocerebral cicatrix as in association with tumor of the brain.

Pathologic Anatomy.—Meningocerebral Cicatrix: Posttraumatic cicatrization of the brain following open wounds (fig. 5 *A*) has been described in detail in another paper (Penfield [44]). The damaged cerebral

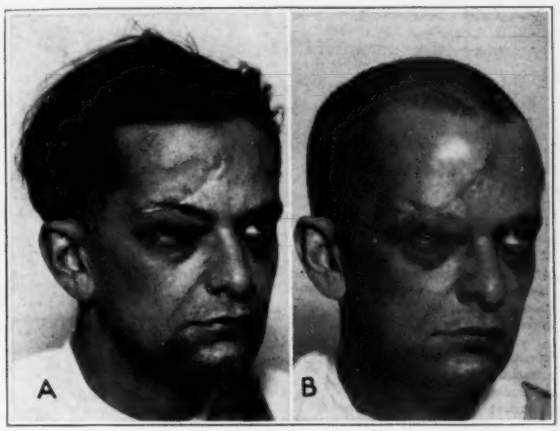

Fig. 5 (M. J.).—The patient was a French Canadian suffering from petit mal seizures and from generalized attacks beginning with loss of consciousness and turning to the left. In *A*, laceration of forehead indicates the site of a blow received sixteen years previously. *B* shows an incision three weeks after operation, 1935.

tissue is progressively absorbed, neuron elements disappearing. There are overgrowth of fibrous astrocytes and ingrowth of connective tissue fibroblasts into this area of destruction of brain tissue. The scar, which is attached to the dura, has a gelatinoid appearance but has tensile strength much greater than that of cerebral tissue, which depends on its vaso-astral framework for such toughness as it possesses. (For such

43. Schou, H.: Trauma Capitis and Epilepsy, Acta psychiat. et neurol. **8**:75, 1933.

44. Penfield, W.: The Mechanism of Cicatricial Contraction in the Brain, Brain **50**:499, 1927.

a case see figure 5, and compare figure 6 *A* with 6 *B* for cicatrization.) The scar penetrates irregularly into cerebral tissue; collagen and astrocyte fibers come to lie somewhat in parallel, and an actual traction is exerted on the vaso-astral framework of the brain, which causes struc-

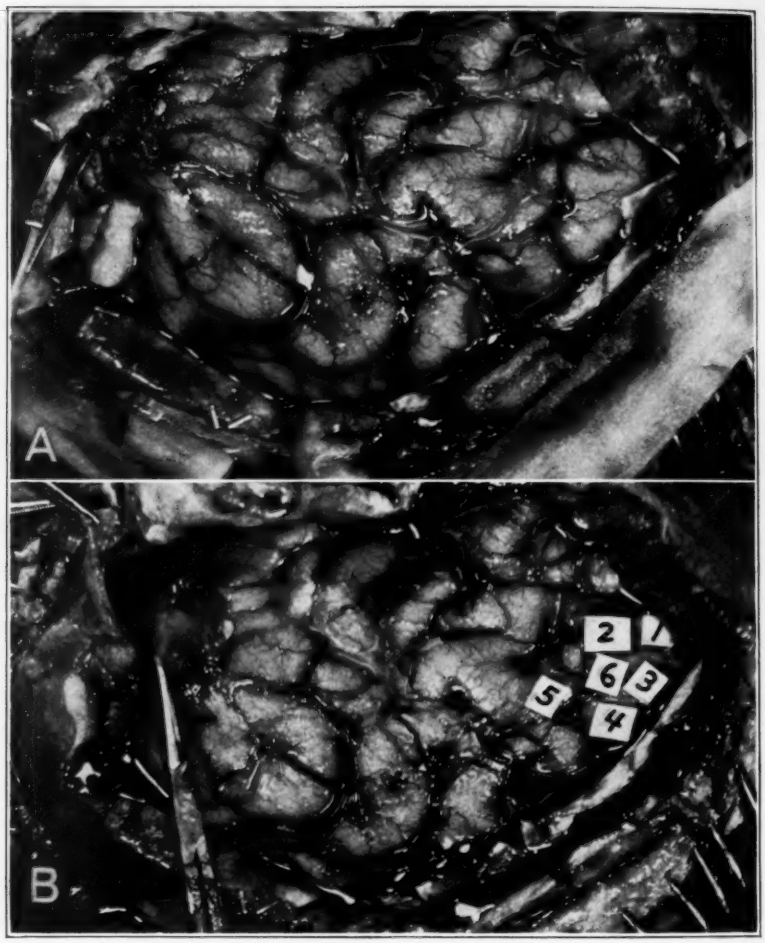

Fig. 6 (M. J.).—After osteoplastic exposure of the right frontal lobe. In *A* the brain is seen to be attached to the under-surface of the dura by a tenacious cicatrix. Scissors indicate the point of attachment. *B* shows the cicatrix freed from the dura. Note the retraction of the brain when relieved from the cicatricial pull. The numbers on the surface of the brain indicate areas from which movement and sensation in the face and in the mouth were obtained.

tures of the brain to be drawn toward the cicatricial attachment, as demonstrated by the wandering of the ventricles. The traction increases year after year, and very old scars, even up to twenty years, show some

evidence of continued destruction of tissue. Progressive cicatricial contraction, progressive local destruction and progressive disappearance of local nerve elements constitute cicatrization in the brain, and this cicatrization may be followed even as long as ten or fifteen years after injury by epileptiform seizures that have their site of origin near the scar.

A priori, radical excision of such a scar (fig. 7 *A* and *B*) would appear to be as clearly indicated as the removal of an epileptogenic tumor, provided the same sort of scar will not reform. As the result of a series of investigations of this problem (Penfield,[45] del Rio-Hortega and Penfield[46] and Penfield and Buckley[47]) it can be stated that clean removal of cerebral tissue is followed by little or no cicatrization. With no destroyed cerebral tissue left to be absorbed, the space

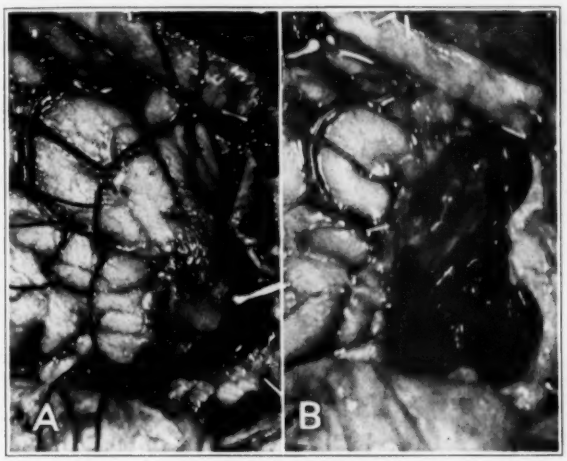

Fig. 7 (M. J.; see figures 5 and 6).—In *A*, silk sutures indicate the site at which removal will occur when they are tied. *B* shows the stump of the frontal lobe and the ventricle widely open.

is filled with cerebrospinal fluid, and rigidity of the skull prevents collapse of the walls of the excised area.

Meningocerebral cicatrix may also result occasionally from a localized abscess of the brain which has become sterile either with or without

45. Penfield, W.: Meningo-Cerebral Adhesions, Surg., Gynec. & Obst. **29**:803, 1924.

46. del Rio-Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278 (Nov.) 1927.

47. Penfield, W., and Buckley, R. C.: Punctures of the Brain: Factors Concerned in Gliosis and in Cicatricial Contraction, Arch. Neurol. & Psychiat. **20**:1 (July) 1928.

drainage, the healed local meningitis having been enough to produce heavy overlying adhesions (fig. 8).

Cerebral Cicatrix: One or more focal areas of atrophy in the brain may result from cerebral contusion without open laceration. The end-result of such a contusion is likely to be an atrophic hollow in the cerebral cortex, usually colored somewhat yellow and moderately adherent to overlying dura (fig. 9 *A, B* and *C*). This is clearly the result of subpial hemorrhage, for I have seen on one occasion such a circumscribed hemorrhage, which resulted from operative trauma at a first operation, converted into a yellowish hollow at a second operation, seventeen months later.

Such areas of focal atrophy, like the atrophy which follows arterial occlusion, may be called cerebral cicatrix, but the amount of connective tissue admixture is very much less than in meningocerebral cicatrix. There may be little or no evidence of cicatricial pull, and the incidence of epilepsy resulting from such lesions must be less than that from meningocerebral cicatrix, as is indicated by the difference in the statistics given for injury to the head with and without penetration of the dura.

Cerebral Atrophy: Simple cerebral atrophy is associated much less frequently with epilepsy than is meningocerebral cicatrix. When such atrophy is the result of circumscribed blockage of a large artery, there may result a well circumscribed area of atrophy in which fibrous gliosis occurs but without adhesion of the dura. At times a cyst comes to replace a circumscribed area of the brain (fig. 10). Localized atrophy may be found after a febrile illness, which may be called meningitis (fig. 11). Such "meningitis" or "encephalitis" usually occurs in children, and it seems likely that the actual process is thrombosis of cerebral vessels secondary to the marked dehydration which may be associated with any acute febrile illness in children. There is often a history of a few convulsions at the time followed years later by epilepsy.

However, a word of warning must be interjected here. Focal (as well as generalized) cerebral atrophy may result from recurring epileptic seizures or, to be more accurate, may result from the vascular spasm which in some instances follows convulsions (Penfield[48]). If these seizures are local ones, the vascular spasm also is likely to be local, with the cerebral destruction also localized. Thus the surgeon may be misled into considering focal atrophy the cause in cases in which it is really the result of the convulsive state.

48. Penfield, W.: Les effets des spasmes vasculaires dans l'épilepsie, Union méd. du Canada **63**:1275, 1934.

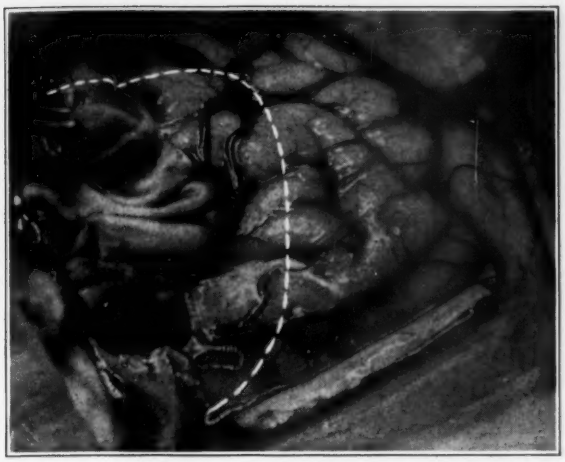

Fig. 8 (M. M.).—An abscess of the right frontal lobe secondary to frontal sinusitis which had been successfully drained ten years previously by Dr. A. W. Adson, of the Mayo Clinic. Epileptiform seizures, apparently generalized, began two years later. Attacks were preceded by turning of the head to the left. Note the dura turned back but firmly attached to the cicatrix within the brain. The site of removal is indicated by the broken line.

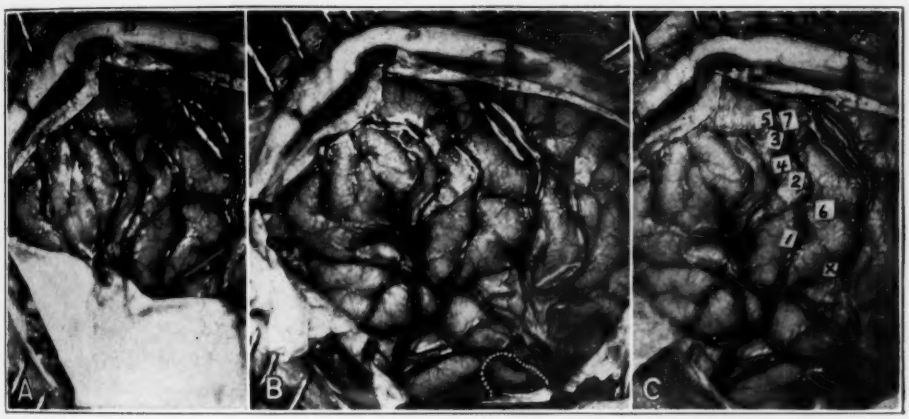

Fig. 9 (F. F.).—The patient was a girl of 19 years. Simple fracture of the skull had occurred nine years previously, and there were epileptiform seizures for five years before operation. An encephalogram showed enlargement of the ventricles but no deviation. Attacks began with a rumbling noise and turning of the head to the left, suggesting involvement of the right temporal lobe. In *A*, note adherence of the dura to the focal area of cerebral atrophy. *B*, the depression after section of the adhesion was seen to be slightly yellow. This area was not touched because of its possible proximity to speech centers, as the girl was left-handed, and because there was no evidence that her attacks had origin here. A second area of focal atrophy, which was also adherent to the dura, is indicated by the white dots and is partly seen in the temporal lobe just below the fissure of Sylvius. *C*, the central sulcus has been outlined as indicated by the numbers, and the epileptogenic focus in the temporal lobe has been removed.

Results of Craniotomies.—During a period of five years [49] my associate, Dr. Cone, and I have carried out craniotomy on 75 patients who could be followed satisfactorily and who were suffering from chronic epileptiform convulsions. All instances of such operation are included in this analysis with the exception that cases of cerebral tumor, acute abscess, recent cerebral hemorrhage and similar conditions have been eliminated from the group.

(*a*) Excision of Meningocerebral Cicatrix: As already pointed out, in most cases the lesion of this type was produced by a wound which penetrated the dura: 6 cases of depressed fracture of the skull, 5 cases of

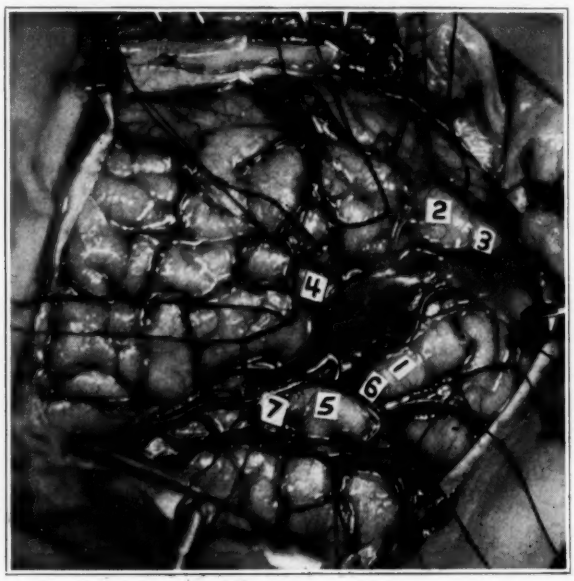

Fig. 10 (J. B.).—The lesion was probably caused by injury at birth. Epileptic seizures were ushered in by dizziness, nausea and turning of the head to the left. Moderate left hemiplegia and hemiatrophy were present. Right osteoplastic craniotomy showed complete focal destruction of a discrete zone which would correspond roughly with the central fissure. There were no adhesions. Strong stimulation failed to produce movement of the contralateral limbs. Stimulation at *3* (the numbers are placed upside down) produced numbness in the opposite hand. Stimulation at *1* and at *6* produced a feeling of dizziness, which the patient said was like the beginning of an attack. Stimulation at *5* produced nausea, which he also said felt like the beginning of an attack. The silk threads were passed deeply into the brain. When they were tied the cyst walls were cut free from the brain. The ventricle was opened widely. No paralysis followed removal, proving that there was migration of control of the left arm and leg to a distance.

49. The period during which these patients have been followed is short, and nothing less than a lifetime is altogether satisfactory. I began to operate on

bullet or shell wounds of the skull and 1 of depressed fracture at birth. There were also 5 cases of severe head injury without obvious depression of bone fragments and 5 cases of healed abscess of the brain.

Of the 22 patients, 2 died, both as the direct result of operation. There was failure in 3 cases, 2 patients being about the same as before operation and 1 having become somewhat worse. Seven patients showed real improvement as regards intensity and frequency of attacks, 1 of these having had only one attack in the year following operation; another had a gunshot wound of both temporal lobes, only one having been operated on as yet. Ten cases (or 46 per cent) may be called instances of complete "cure" so far, as there have been no attacks up to the time of writing for the following periods, respectively: three-fourths; one; one; one and one-fourth; one and one-fourth; one and

TABLE 2.—*Craniotomies for Chronic Convulsions*

	Number of Patients	Percentage "Cured"*	Percentage Improved	Percentage of Failures
a Excision of meningocerebral cicatrix	22	46	32	23
b Excision of focal cerebral cicatrix or focal atrophy	22	41	32	27
c Exploration without excision	24	8	12.5	79
d Ligation of cerebral arteries	4	25	0	75
e Evacuation of subdural fluid	3	33	33	33
Total craniotomies	75	32		
(Operative deaths 2—2.6 per cent)				

* The word "cured" is used to indicate that the patient has had no seizure since leaving the hospital up to the time of this analysis. The phenobarbital or other antispasmodic drug which the patient was receiving before operation is continued after operation for a year or two in gradually decreasing doses and then withdrawn completely.

one-half; two and three-fourths; three and one-fourth; six and one-half, and seven years.

None of these patients have suffered serious functional defects as the result of radical extirpation. There is no postoperative paresis, although a number of patients have homonymous defects in the visual fields or loss of cortical sensibility in one extremity, according to the location of the extirpation. Fourteen of the patients are working or attending school full time. Two others are capable of satisfactory work if they can secure positions. The apparent cures are distributed among the cases of different types of injury as follows: 3 cases in which the condition was secondary to abscess, 2 of depressed fracture, 2 of head injury without depression, 1 of birth trauma and 2 of bullet wound.

epileptogenic cicatrices, following the example of Otfried Foerster, in 1928, and my indebtedness to him is obvious. Five years before that date I had begun to study cerebral scarring with the possibility of such operations in view, and this analysis was furthered by Pio del Rio-Hortega, whose help I sought during the pathologic study.

(*b*) Complete and Incomplete Excision of Focal Cerebral Cicatrix or Area of Focal Atrophy: There are 22 cases under this heading. These cerebral lesions were the result of a variety of abnormal causes. In 6 instances the cause was definitely trauma to the head. In 7 others the cause was probably trauma. In 1 the cause was meningitis, and in another a heavy arachnoidal plaque was present but the cause was not evident. In 1 instance the cause was embolism, and in 3 it was quite unknown. In 3 others, of which the etiology was unsettled, there was diffuse atrophy, and the excision was an attempt to remove the trigger zone only.

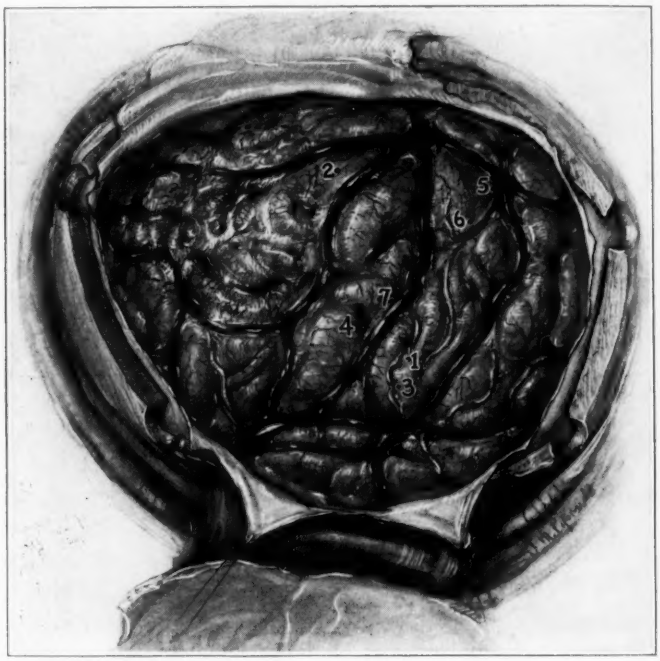

Fig. 11 (D. S.).—The patient, a boy of 17, had a severe febrile illness at the age of 11 years, with meningism. Epileptic seizures had occurred for three years, characterized by rotation of the eyes and head to the right followed by convulsive movements of the right arm, hand and leg and then by generalized movements. Note the localized area of atrophy in the frontal lobe within the dots.

At *1* stimulation caused swallowing; at *2* it caused the eyes to turn upward and to the right. This was repeated. At *3* stimulation produced sensation in the right side of the jaw and tongue (?) and swallowing. At *4* it caused the eyes to turn upward and to the right, continuing one-half minute after the cessation of the stimulation. The stimulation was repeated without result. At *5* stimulation caused extension of the right hand, which was repeated. At *6* stimulation caused clonic closure of the right hand, and at *7*, twitching of the right side of the mouth.

The excision extended somewhat beyond the tissue indicated by the dotted black line.

It must be further recalled that, as already pointed out, atrophy, either generalized or focal, may be partly or wholly secondary to the vascular spasms which sometimes are associated with recurring seizures.

Among these patients there were no deaths. In 6 instances the operation was a failure, 4 patients being the same as before operation or slightly improved and 2 having gradually grown worse. Of these 6 cases of failure, the cause of the atrophy was unknown in all, and it therefore was possibly secondary to the anemia following the attacks and not primary. Nine patients were definitely improved, 1 of them having had only one attack in four years; another has had only two mild seizures in the four years since operation, both of which occurred at the time of an attack of measles. Seven patients are apparently cured, having been completely free from attacks for three-fourths; two; two; two; three; four, and five years, respectively, since operation. If the 2 cases of four years' duration just mentioned were added to the instances of "cures," there would be 9 "cures," or 41 per cent.

Thirteen of these patients are working full time or are regularly attending school.

(*c*) Exploration Without Excision: There are 24 cases in this group in which nothing was done to the brain. In 18 the operation caused no improvement, and 3 or 4 patients are now somewhat worse, 1 of them believing that the operation caused him to have more frequent seizures. Three patients profess to be improved by the operation, although the improvement is not very impressive in 2. The third, however, has had only two attacks in two and one-half years. Two patients have been "cured" for one and one-half and five years, respectively.

There were no deaths from operation in this group, but there were 4 patients who died, one-fourth, two, three and four years, respectively, after operation. All these patients showed cortical atrophy at the time of exploration. Two of the 4 patients were proved definitely to have deep-seated neoplasm, and the other 2 almost certainly had the same condition. These patients seem to form a characteristic group. The atrophy of the convolutions without increase of pressure and with little deformity of the ventricles is evidently due to cerebral ischemia, resulting from obliteration of cerebral arteries by the tumor deep in the hemisphere. Thus at first the atrophy more than compensates for the space occupied by the tumor. In all 4 patients the seizures came on in adult life and were obviously focal.

In 14 of the cases a generous decompression was made beneath the temporal muscle when the bone flap was replaced, and the dura over the temporal lobe was left open. In the remaining 10 decompression was not made. One case of "cure" and 2 of improvement fell in the group

in which decompression was carried out, while the case of five year "cure" and 1 case of improvement were among those in which there was no decompression.

(*d*) Ligation of Cerebral Arteries: Pial arteries were ligated three times. Twice arteries to focal areas of atrophy were ligated, and it must be admitted that in neither instance was there any real indication of abnormality of vascularization, and in retrospect excision might have been better advised. In both these instances the procedure was a failure. In the third there were unusual indications for such a procedure, which may be described in detail.

W. O., a boy aged 19, had seizures involving the right side from the age of 13 years. There was slight comparative atrophy of the right side of the face, and

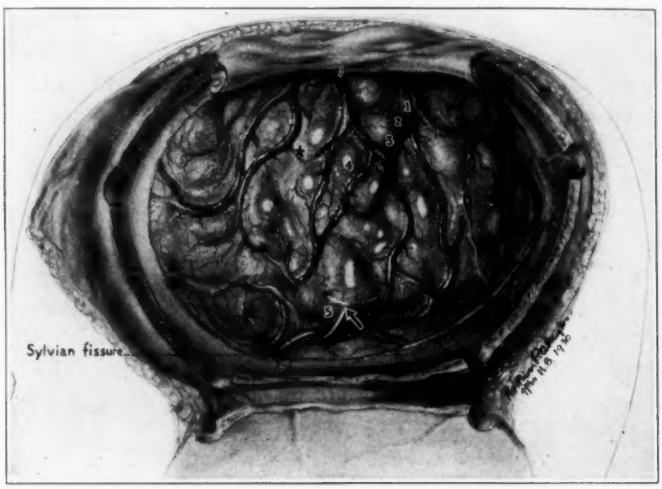

Fig. 12 (W. O.).—This case is described in the text. Osteoplastic craniotomy was performed on the left side. The numbers indicate the precentral gyrus. Faradic stimulation at the star produced a jacksonian seizure characteristic of the patient's habitual attacks. The discrete patches of anemia appeared after the seizure was over. The artery indicated by the arrow was tied.

attacks were precipitated by efforts at concentration. When the left hemisphere was exposed, moderate convolutional atrophy was found in the parietal lobe. After the fissure of Rolando had been outlined by stimulation (*1, 2, 3, 4* and *5*, fig. 12) an attack on the right side was induced by faradic stimulation at the point indicated by the star in the same figure. The attack was said by the patient and by several observers to resemble those from which he habitually suffered.

After the seizure there appeared small snow-white areas of anemia on a number of convolutions, as indicated in figure 12. These areas lay roughly in what seemed to be the portion of the cortex vascularized by a large artery, indicated by an arrow, which passed upward from the fissure of Sylvius. Professors W. Spielmeyer, Rawle Geyelin, Stanley Cobb and Colin Russel were present at the opera-

tion, and after a general consultation it was decided that ligation of the artery, in spite of its relation to the speech area, was justifiable. This was done. During the following ten days the patient had severe motor aphasia and marked apraxia of the right hand. At the end of that time he suffered a series of focal seizures involving the right hand and the right side of the face. The attacks were associated with improvement of function and were followed by rapid complete recovery of speech and of motor control of the hand.

In the five years which have followed there have been no seizures and no complaints of any sort. The use of phenobarbital was decreased gradually and was discontinued two years after operation.

(*e*) Evacuation of Subdural Fluid: These cases have already been discussed and described. Drainage of the trapped subdural exudate was sufficient to give complete relief to 1 patient for five years up to the time of writing, while the second was greatly improved in the four and one-half years since operation, having had three attacks only, all at times of illness. The use of phenobarbital had been discontinued and he was working at the time of writing. The third patient was relieved temporarily only, his attacks having been present a long while before operation.

SUMMARY AND COMMENT

Surgical therapy demands the most exhaustive preliminary study of the pathologic anatomy involved, and no surgical procedure should be countenanced unless it is directed by rational analysis of the individual etiologic problem. In idiopathic epilepsy each seizure is probably initiated by a discharge in the gray matter, which is just as focal as that in the cases of epileptiform seizures which result from a gross lesion of the brain. There may be nothing in the outward manifestation to distinguish one form of convulsion from the other. But the initial clinical problem is to discover whether or not a gross lesion exists in the brain as well as what pathologic influences may play on it. When history, examination or pattern of attack suggests the possibility of a focal lesion, an encephalogram should be made and an attack observed.

In essential epilepsy there is no gross organic defect of the brain, but there is nevertheless a common organic abnormality, which may be described as cerebral vasolability. This irritability of cerebral vessels is found also, although to a less extent, in focal epilepsy with a gross lesion of the brain.

Conclusions regarding the more important methods of surgical treatment proposed for essential epilepsy may be summarized as follows:

1. Cervicothoracic sympathetic ganglionectomy has failed, except perhaps in the occasional case in which the condition is associated with obvious abnormality of the sympathetic nervous system.

2. Removal of the carotid body and denervation of the carotid sinus are as yet without theoretical justification except in the rare case of demonstrably abnormal carotid sinus reflex. Nevertheless, the practical results secured by Lauwers demand further consideration.

3. Subtemporal decompression should be carried out only occasionally as an incident to craniotomy undertaken for other purposes or in the rare instances of chronic collection of fluid in the subdural space, in which case the procedure may result in cure.

4. Spinal insufflation of air or oxygen in our clinic has been effective as a therapeutic measure only for patients under 16 years of age whose seizures have occurred for four years or less.

Epileptiform seizures secondary to lesions of the brain may appear at any age, but when they make their first appearance in adult life the cause is tumor or cicatrix in the majority of instances in my experience. Such cases call for surgical therapy. The incidence of epileptiform seizures among patients with tumor of the brain is about the same as the incidence among patients who have meningocerebral cicatrix from a perforating injury to the brain, although the figures from different clinics vary. On the other hand, in my experience the operative excision of such cicatrices and of areas of focal atrophy gives an even better result from the point of view of cessation of attacks than does radical extirpation of the more benign types of tumor.

My results (table 2) are as follows: After radical excision of meningocerebral cicatrix (22 cases) 46 per cent of the patients have remained attack-free and 32 per cent are markedly improved. After radical excision of areas of focal atrophy and focal cerebral cicatrix (22 cases) 41 per cent of the patients are attack-free and 32 per cent are improved. The figures for the two most favorable subtypes of brain tumor (table 1) may be compared with these, selecting only those instances in which seizures were present before operation and in which the patient could be followed satisfactorily up to the time of writing. There were 12 such patients with meningeal fibroblastoma, of whom 5, 42 per cent, became attack-free after operation. Most of the remaining patients had fewer seizures than before operation. There were 16 patients living after removal of a cerebral astrocytoma who had seizures before operation, of whom only 2 are attack-free (12 per cent) although most of the others are much improved in regard to attacks.

This analysis of cases of tumor and the analysis of the cases of cicatrix cover the same time range of approximately six years, and the operations were carried out in both instances under the same conditions. For epileptiform seizures, exclusive of those with which neoplasm, abscess or hemorrhage of the brain were associated, there have been in all 75 major craniotomies during this period, with 2 operative deaths.

In spite of the fact that these 75 operations include the negative explorations, 32 per cent of the total number of patients are free from attacks and 23 per cent are definitely improved.

The most frequent cause of cerebral scars is trauma (including injury at birth), which may precede the onset of seizures by from one to fifteen years. Operable cicatrix may also result from the healing of an abscess, from local meningitis and even from vascular occlusion.

For discriminating radical operation a wide osteoplastic exposure should be made, so that the exploration may be ample. To open a subarachnoid collection of fluid (fig. 13) is to do nothing of therapeutic value. When removal is undertaken, the line of excision should be

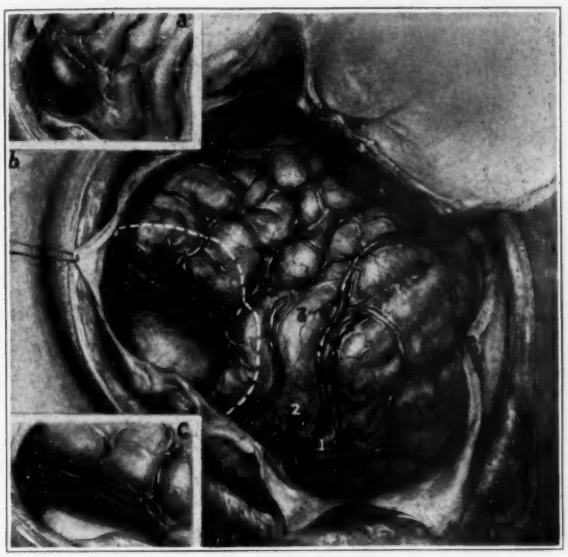

Fig. 13 (H. P.).—The patient was a girl of 15. There was no clue as to the cause of seizures. Attacks began with aura in the opposite foot. Osteoplastic craniotomy was performed on the right side. Inset *a* shows the appearance when the dura was first opened. Stimulation at *1* produced a reaction in the toes, at *2* in the elbow, and at *3* in the hand. There were no adhesions. At the first operation the cyst was simply opened, which resulted in no improvement in symptoms. A year later the wall of the cyst was removed as indicated by the broken lines. This has been followed by five years of freedom from attacks up to the time of writing.

made through normal surrounding brain no matter what type the cicatrix may be (see dots in figs. 11 and 13 and threads in figs. 7 *B* and 10). The removal must leave no damaged tissue behind (fig. 7 *A*) and, when easily possible, should enter the ventricle. Such an excision leaves a fluid-filled space, with little or no scarring. This excision should be preceded by painstaking electrical exploration of the cortex

under local anesthesia and should be carried out only when the evidence indicates that the location of the area in question corresponds with the pattern of convulsive seizure from which the patient suffers.

Spontaneous arrest of habitual seizures is not an unknown phenomenon in essential epilepsy. But this spontaneous cessation never occurs when there is a definite objective lesion of the brain, at least as far as my own experience goes. The 2 patients with essential epilepsy who have been relieved of their attacks (for one and one-half and 5 years) among 24 in our series in whom exploratory craniotomy gave negative results, might quite well be considered as presenting examples of such spontaneous arrest. In neither of these patients was any pathologic lesion seen. Although the evidence may not justify craniotomy for essential epilepsy alone, nevertheless in certain cases the evidence makes it advisable to carry out an exploration in the hope of finding a discrete lesion even at the risk of a negative exploration.

It is obvious that epilepsy can never be certified as cured. Former sufferers must always be considered potentially epileptic, and an illness with high fever may bring on a seizure in such a person years after the apparent cessation of the malady. The "cures" listed can therefore not be considered final, but the result is none the less gratifying to the patient.

As Hughlings Jackson pointed out, there is only one physiologic cause of epilepsy, but there are many pathologic causes. It is for the physician to search out the pathologic cause and to treat each patient with discrimination. There is no panacea, no universal remedy.

PARAPHYSIAL CYSTS

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Paraphysial cysts were first tentatively identified as such by Sjövall [1] in 1909, but since that time the etiology in reported cases of these "colloid cysts of the third ventricle" has received either neglect [2] or only irresolute attention. This might possibly be due to the fact that the cysts are comparatively rare (only forty-seven being reported in the literature of the past three quarters of a century, with but nine successful removals) or to the evident facility with which they may be confused pathologically with cystic degeneration of the choroid plexus when given only perfunctory consideration.[3] Both preoperative diagnosis and curative therapeusis being now possible, the origin and adequate identification of these cysts should no longer remain shrouded in doubt.

PHYLOGENIC CONSIDERATION

The boundaries of the third ventricle, as the rostral portion of the primitive neural tube, have been the ancient proving ground for many phylogenic experiments and are remarkable for the rich diversity of structures which have arisen from the invaginations and evaginations occurring there. The results of these exist in the adult human being not only as well-developed and highly-specialized organs but also as use-

From the Department of Surgery, Multnomah County Hospital, and the neuropathologic section of the Department of Pathology, the University of Oregon Medical School.

1. Sjövall, E.: Ueber eine Ependymcyste embryonalen Charakters (Paraphyse?) im dritten Hirnventrikel mit tödlichem Ausgang: Zugleich eine Beobachtung wahrer lipochromer Veränderungen mit Auftreten von "Halbmondkörperchen," Beitr. z. path. Anat. u. z. allg. Path. **47**:248, 1909.

2. Masson, C. B.: Complete Removal of Two Tumors of the Third Ventricle with Recovery, Arch. Surg. **28**:527 (March) 1934.

3. (*a*) Drennan, A. M.: Impacted Cyst in Third Ventricle of Brain: Report of Two Cases, Brit. M. J. **2**:47, 1929. Such cystic degeneration of the choroid plexus was recognized as "not unusual in lateral ventricles, but apparently rare in the third ventricle." (*b*) Fulton, J. F., and Bailey, P.: Contribution to the Study of Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, 145 and 261, 1929. (*c*) Zimmerman, H. M., and German, W. J.: Colloid Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **30**:309 (Aug.) 1933.

less microscopic vestiges and rudiments occasionally giving rise to bizarre tumors.[4] Wilder [5] wrote:

> The sporadic occurrence of these vestigial sense organs which . . . cannot be of the slightest use, points definitely to the presence of similar organs in a functional condition in some remote ancestor. That these parts were organs of vision there can be but little doubt, and there are certain indications which lead us to think that they were once paired, although always close together. Beyond this, investigation has as yet shown nothing, and the whole subject remains at present one of those half-completed histories, of which the record consists of a few poorly preserved fragments.

The most anterior of the vestigial structures arising from the midline roof of the third cerebral ventricle is the paraphysis.

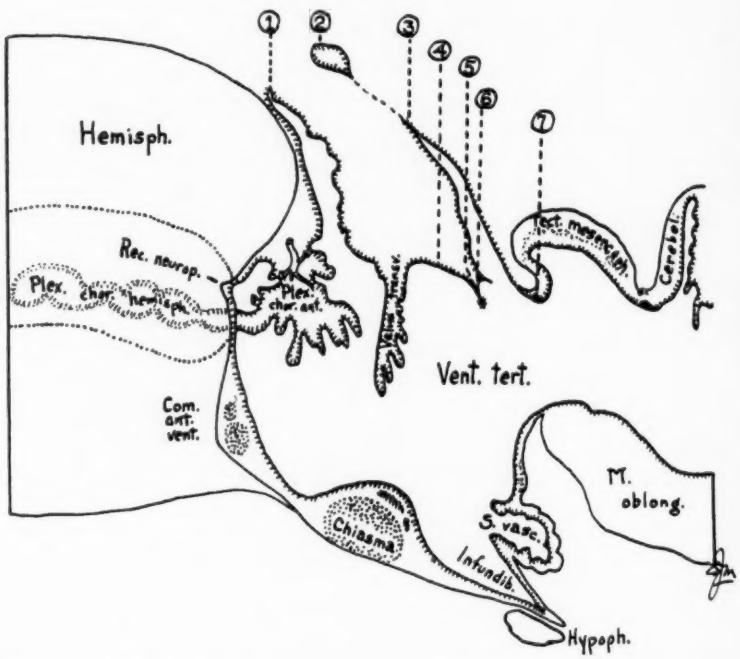

Fig. 1.—Idealized schema of the structures of the third ventricle in lower vertebrates (fish) in midsagittal section, after Edinger;[6] compare with figure 4. *1* indicates the paraphysis; *2*, parietal organ; *3*, epiphysial stalk; *4*, dorsal sac (the postvelar tubules[13] are superiorly directed digitations of the most anterior part of this structure); *5*, habenular commissure; *6*, parietal sac; *7*, posterior commissure.

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4. McLean, A. J.: Pineal Teratomas, with Report of a Case of Operative Removal, Surg., Gynec. & Obst. **61**:523, 1935.

5. Wilder, H. H.: The History of the Human Body, ed. 2, New York, Henry Holt & Company, 1923, p. 477.

The paraphysis has been described only in vertebrates; I have found no mention of it in lower chordates. Edinger,[6] in describing structures of the roof of the 'tween-brain (fig. 1), passing backward from the recessus neuroporicus, and the choroid plexus, said:

". . . one next encounters there in nearly all vertebrates a dorsally directed outpouching of the plexus formation making a red vascular nubbin which lies above the brain within the cranial chamber. This pocketing was called the paraphysis by Selenka.[7] Its function is wholly unknown, but it cannot be useless for in the ganoids and some amphibia (*Ichthyophis* Burckhardt) it enlarges to a complicated structure. The simplest form of the paraphysis, an epithelial pouch at the superior part of the lamina supraneuroporica, is found in *Petromyzon*. . . . In most teleosts the paraphysis is only poorly developed; and this is also true in

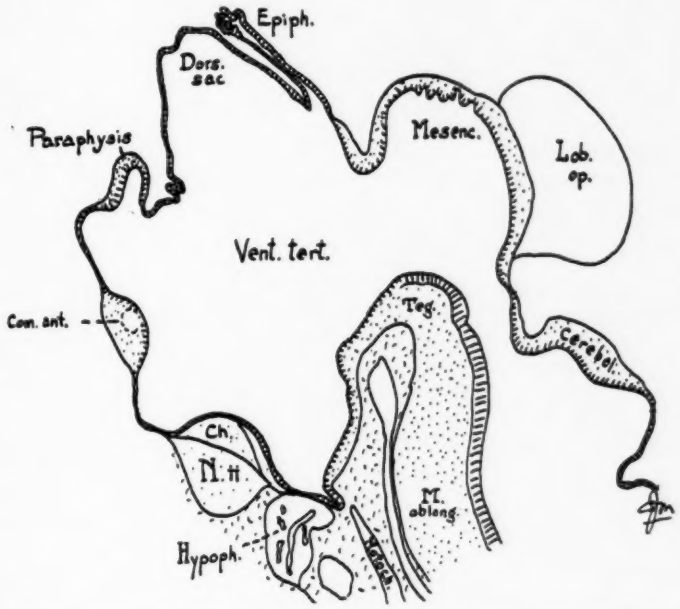

Fig. 2.—Midsagittal section of the structures of the third ventricle of the embryonic chick, showing the paraphysis (after von Kupfer [9b]).

selachians, although in *Chimaera* a considerable mass is formed. It is enormously developed in the ganoids; in them (*Amia*, and especially *Lepidosteus*) one finds multiple small winding acini immediately before the velum transversum which, with their rich vascularization and cuboid epithelium, are quite reminiscent of glandular structure. . . ."

6. Edinger, L.: Vorlesungen über den Bau der nervösen Zentralorgane des Menschen und der Tiere, ed. 7, Leipzig, F. C. W. Vogel, 1908, vol. 2, p. 203.

7. Selenka, E.: Das Stirnorgan der Wirbeltiere, Biol. Centralbl. **10**:323, 1890-1891.

Eycleshymer and Davis [8] described "considerable pigment" as occurring in the single layer of thickened columnar epithelium which composes the posterior wall of the embryonic paraphysis in the mudfish, Amia. Starting as a simple pear-shaped vesicular evagination of cuboidal epithelium, symmetrical lobes again evaginate distally therefrom and then digitate into "numerous foldings and diverticula," nerve fibers not being observed. Kingsbury [9a] noted that the columnar epithelium of the ganoidal paraphysis was "of a different appearance, and easily distinguishable from the cells of the dorsal sack and the membranous roof" of the 'tween-brain; they had "indeed the appearance of secreting cells,

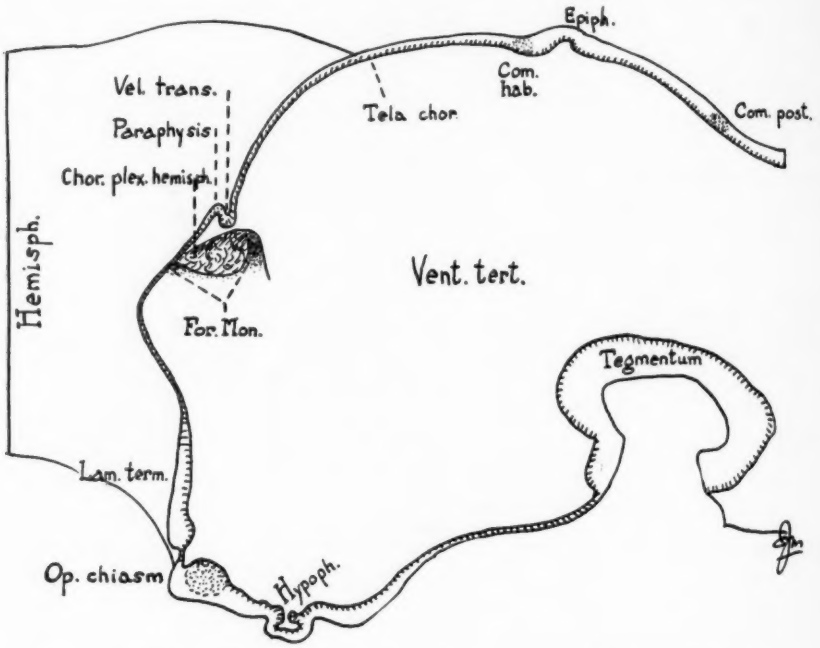

Fig. 3.—The paraphysial arch and its relation to the roof of the third ventricle in a 19 mm. human embryo seen in midsagittal section (redrawn from a halftone depiction of a wax-plate reconstruction published by Bailey [12]).

but of a nature different from those of the surrounding epithelium." The difference was not further described, but it is readily observed in figure 4.

8. Eycleshymer, A. C., and Davis, B. M.: The Early Development of the Epiphysis and Paraphysis in Amia, J. Comp. Neurol. **7**:45, 1897.

9. (*a*) Kingsbury, B. F.: The Encephalic Evaginations in Ganoids, J. Comp. Neurol. **7**:37, 1897. (*b*) von Kupfer, K.: Die Morphologie des Centralnervensystems, in Hertwig, O.: Handbuch der vergleichenden und experimentellen Entwicklungslehre der Wirbelthiere, Jena, Gustav Fischer, 1905, chap. 8, pt. 2.

The paraphysis has received only casual attention in most textbooks on human embryology,[10] and in textbooks on human anatomy exact descriptions are limited to lower orders.[11] Bailey's [12] research in 1916 on the roof plate of the human telencephalon (fig. 3), however, disclosed that:

> The paraphysal arch can be followed [from the 19 mm. embryo] to the embryo of 32 mm. as an arch of the roof plate of the telencephalon. It lies just anterior to the velum transversum and from its side arise the lateral choroid plexuses. The anterior pouch of the choroid plexus of the third ventricle lies in the diencephalon and is not, therefore, homologous to the paraphysis of the lower vertebrates. No indication of the development of a glandular structure was found.

The paraphysis was depicted by him as a simple nonracemose and nonrugous evagination.[13] Concerning its relations to the choroid plexus, he added that ". . . in urodele Amphibia it is between the paraphysis and the tenia fornicis that the lateral choroid plexus makes its appearance pushing into the ventricle . . ." and that in human material "the lateral choroid plexus never approaches the midline except along the sides of the paraphysal arch anterior to the velum transversum . . ."

STRUCTURE AND RELATIONS

In view of the fact that the paraphysis is an evagination of an ependyma-lined structure, one would expect it to present a single layer

10. For instance, Streeter's description (in Keibel, P., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912), stated: ". . . the roof plate . . . consists of a thin ependymal plate uniting the two thalamic plates. At the fourth week it is smooth. Proliferation of its cells causes it to expand and form an outward ridge which is soon thrown into longitudinal folds. . . . These folds project into the ventricle as the ectodermal lining of the tela choroidea of the third ventricle. . . . Orally this . . . is continued into the telencephalon where it forms a pointed pouch overlapping the lamina terminalis and the contained commissures. . . . The anterior choroidal pouch apparently corresponds to the paraphysis of the lower vertebrates." Both Warren [13] (1917) and Bailey [12] (1916) have refuted this not uncommon former confusion of the sacs of the choroid plexus with the paraphysial evagination.

11. Poirier, P., and Charpy, A.: Traité d'anatomie humaine, ed. 3, Paris, Masson & Cie, 1912, vol. 3, p. 49. Ranson, S. W.: The Anatomy of the Nervous System, ed. 2, Philadelphia, W. B. Saunders Company, 1925, p. 31. Ariëns-Kappers, C. U.: Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen, The Netherlands, de Erven F. Bohn, 1921, vol. 2, p. 1031.

12. Bailey, P.: Morphology of the Roof Plate of the Forebrain and the Lateral Choroid Plexuses in the Human Embryo, J. Comp. Neurol. **26**:79, 1916.

13. John Warren (The Development of the Paraphysis and Pineal Region in Mammalia, J. Comp. Neurol. **28**:75, 1917) stated that the "paraphysis is found definitely developed in sheep embryos only [among mammals]. In all other mammalia except man it is represented merely by the paraphysal arch. . . . In human embryos it can be found in occasional cases as a rudimentary and very inconstant structure." See also my figures 5 and 6 and footnote 16*c*.

of cilated epithelium on its internal cystic surface and to possess an outer layer of fibrous stroma analogous to the *Adergeflecht*, two fused layers of which theoretically compose the tela choroidea (velum interpositum). The descriptions of material from human embryos and lower vertebrates just quoted mentioned only cuboidal and columnar epithelium, but figure 4, taken from original preparations of the ganoidal

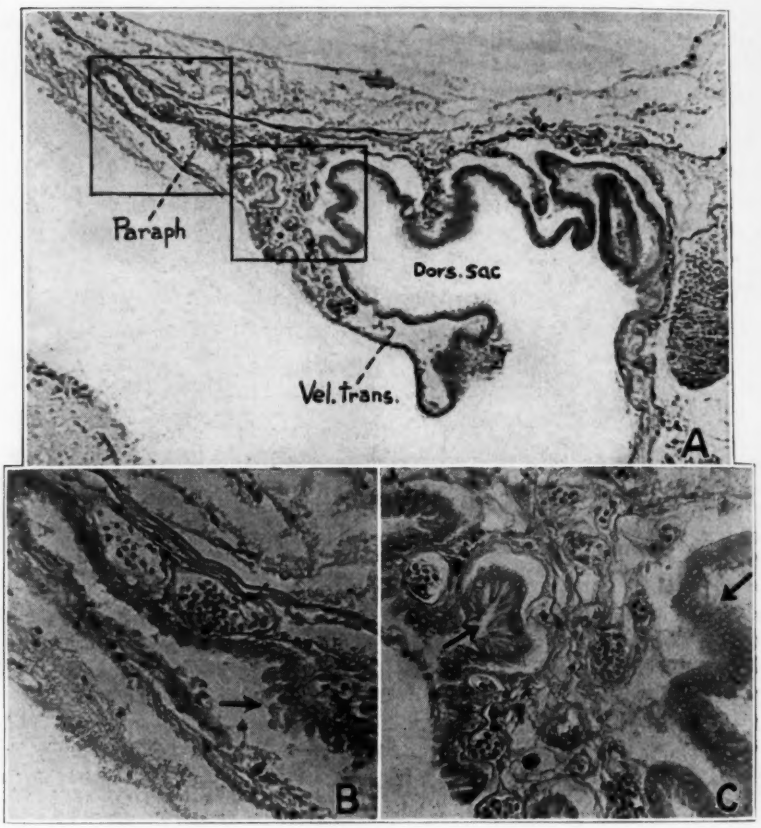

Fig. 4.—*A*, photomicrograph (× 75) of a midsagittal section of the membranous roof of the third ventricle of a ganoid, showing the paraphysial sac, velum transversum and dorsal sac. Hematoxylin and eosin stain. *B*, enlargement (× 250) of the upper squared area in *A* to show the cuboidal and ciliated epithelium (arrow) of the posterior wall of the paraphysis. *C*, enlargement of the lower squared area to show not only the shaggy cilia of the paraphysis but also its characteristic cytoplasmic difference from the stubby and matted ciliated epithelium of the dorsal sac. Courtesy of Dr. William F. Allen.

roof plate, shows the expected abundance of cilia, present not only stubbily in the dorsal sac but also as luxuriant matted fronds in the paraphysial pouch. Although cystic enlargements of the paraphysis

present superiorly into the membranous tela above the ventricle at the onset of their occlusion and enlargement, and indeed are so demonstrated in figure 6 *A*, their extension in this direction is soon limited by the overlying pillars and bodies of the fornices. Then, augmented by the

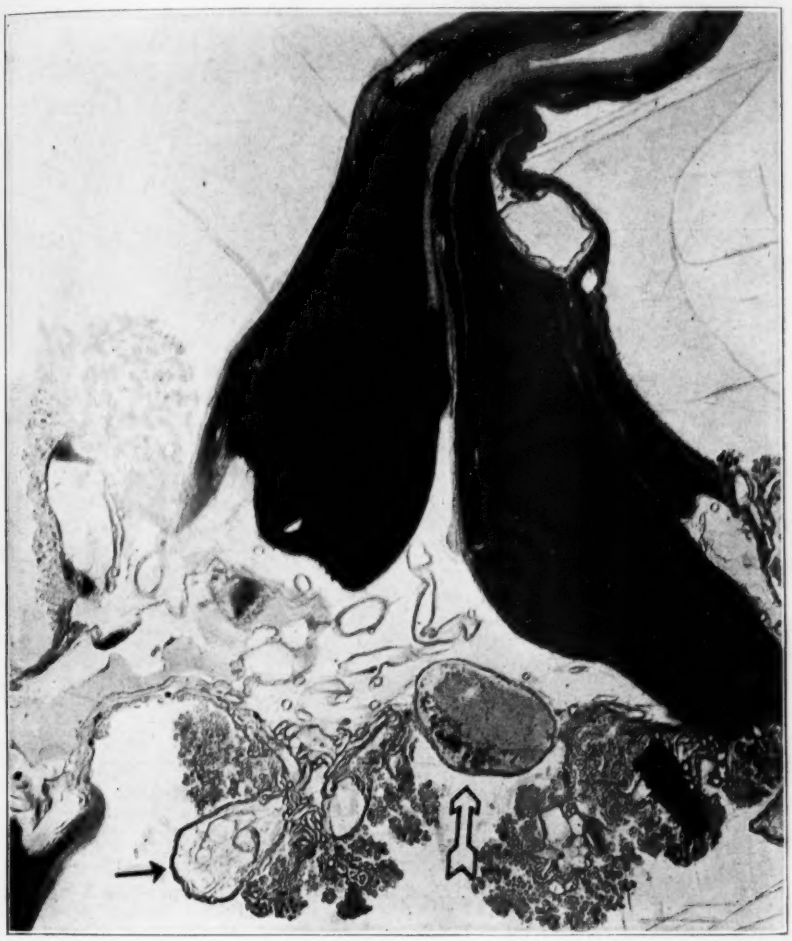

Fig. 5.—Photomicrograph of a coronal section of the roof of the third ventricle of a hydrocephalic child, showing an early stage of a paraphysial cyst (hollow arrow), lying between the two rows of fringes of the choroid plexus in the third ventricle and within the tela choroidea (velum interpositum) underneath the ascending fornical pillars; an enlargement is shown in figure 6 *B*. It should be contrasted with the cystic degeneration of the choroid plexus indicated by the small arrow. Weigert preparation; × 10. Tower brain, slide 600; courtesy of Dr. Adolf Meyer, Baltimore.

gravitational pull of their own increasing weight, they sag downward through the velum to hang pendulous within the lumen of the third ventricle, carrying with them an outer investmental layer of the adult tela. They should thus present, on nearly their entire surface, two layers of tela, back to back as an outer stroma, and should possess an inner lining composed of ciliated epithelium; the double layer of tela should be absent only within the broad basal pedicle, when the latter is present. Caught between the two layers of tela and coursing posteriorly in a more or less symmetrical arc over the lateral surface of the enlarging cyst are the small vessels of the choroid plexus granulations of the roof of the third ventricle; these should not be present

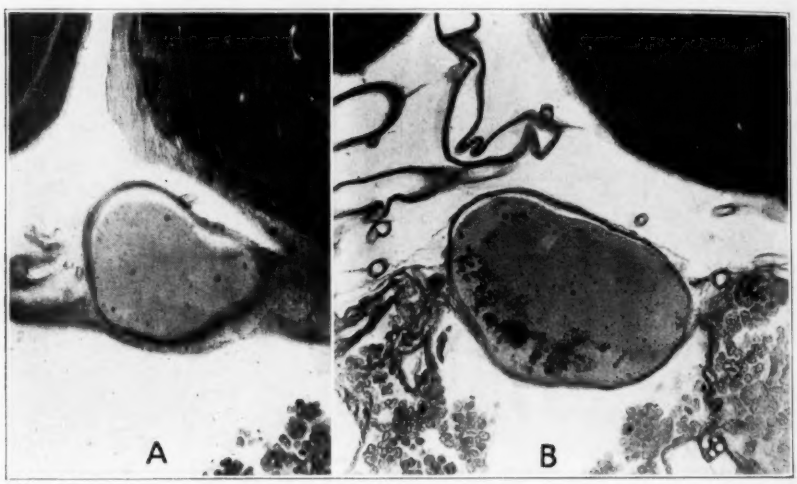

Fig. 6.—Photomicrograph of coronal sections of the tela of the third ventricle, showing in *A* the anterior portion of a small cystic paraphysis lying above the velum and entirely dissociated from the choroid plexus and in *B*, about 0.5 mm. caudad to *A*, the larger cross-section of the cyst as it is suspended in the velum. Note the thick colloid content, the pigment and the lack of trabeculation and contrast with figure 13. The sections are from the same brain as that shown in figure 5. Weigert preparation; × 18. Slides 590 and 600; courtesy of Dr. Adolf Meyer.

on the rostral aspect, or prow, of the cyst; similarly, the vascularity of the capsule should diminish the farther the points of the wall recede from the pedicle and the plexus.

Such a priori theoretical stipulations have been independently substantiated in fragments by the histologic descriptions of various observers. The presence of a ciliated epithelial lining, of cuboidal or columnar epithelium in a single layer (unless cut obliquely), has been noted in

practically all cases in which a careful examination was made,[14] except when the wall of the cyst was necrotic or greatly distended.[15] Neuroglia is not present in the wall [14b] but has been observed in a few instances as an anterodorsal cap external to the collagenous wall within the pedicle lying between choroid plexuses, and it has been postulated, therefore, to be derived from the superjacent fornix.[16] The unabraded bellying inferior wall of the cyst, below the plexuses, often contains a patch of "low cubical epithelium, without blepharoplasten and cilia, that is indistinguishable from the choroidal epithelium," [14b] though elsewhere "the ventral surface of the wall of the cyst (usually) terminates externally in the collagen of which it is composed. The connective tissue, or telar, layer, varying in thickness (and interpretation), is invariably present. The festoons of choroid plexus are usually arranged symmetrically on the lateral walls but may be asymmetrical.[17] Infrequent capillaries "lose themselves in the connective tissue layer of the cyst wall" [17a] and become smaller as they progress from the pedicle.[1] Rarely the tumor does not gravitate downward but forces its way from the tela between the fornices into the cavum septi pellucidi,[15] or may only

14. (*a*) Sjövall.[1] (*b*) Byrom, F. B., and Russell, D. S.: Ependymal Cyst of the Third Ventricle, Lancet **2**:278, 1932. (*c*) Beutler, A.: Ueber Ependymcysten im dritten Ventrikel als Todesursache, Virchows Arch. f. path. Anat. **232**:358, 1921. (*d*) Rinder, C. O., and Cannon, P. R.: Impaction of a Neuro-Epithelial Cyst in the Third Ventricle of the Brain, Arch. Neurol. & Psychiat. **30**:880 (Oct.) 1933.

15. Hassin, G. B., and Anderson, J. B.: Cystic Tumor of the Third Ventricle, U. S. Vet. Bur. M. Bull. **6**:56, 1930.

16. (*a*) Apparently because of a somewhat similar finding, Pollock (Tumor of the Third Ventricle, J. A. M. A. **64**:1903 [June 5] 1915) stated that in his case the tumor was "an encapsulated colloid cyst originating from a glioma," although recognizing its probable "ependymal origin." (*b*) H. Josephy (Ueber einige seltene klinisch und anatomisch interessante Hirntumoren, Deutsche Ztschr. f. Nervenh. **74**:234, 1922) found an associated nodule of spongioblastoma with his paraphysial cyst. (*c*) T. J. Putnam (The Intercolumnar Tubercle: An Undescribed Area in the Anterior Wall of the Third Ventricle, Bull. Johns Hopkins Hosp. **33**:181, 1922) in describing a structure probably representing the vestigial paraphysis, occurring normally in some cats, rabbits, monkeys and men, noted that much of the stroma fibrils in the vascular tubercle resembled mesodermal reticulum rather than neuroglial fibrils, but he also found embedded therein large triangular cells with apparent neuronal nuclei. J. L. Pines (Ueber ein bisher unbeachtetes Gebilde im Gehirn einiger Säugetiere: Das subfornicale Organ des III Ventrikels, J. f. Psychol. u. Neurol. **34**:186, 1926), describing the same structure in the hedgehog, mouse, dog and lemur, also mentioned finding a blending of glial and mesodermal structure in which uncharacteristic parenchymal cells with large nuclei were embedded.

17. Byrom and Russell.[14b] Pollock.[16a]

17a. Drennan.[3a] Beutler.[14c]

bulge the telar roof of the ventricle downward behind the fornical pillars, the cyst then being suspended on the lesser galenic veins.[18]

The content of the cyst is usually unorganized, turbid, milky, tenacious colloid material, with generous flecks or streaky blobs of yellowish-brown, soft, diffluent pigment. When there has been hemorrhage, old blood pigment may be present, or the colloid may be stained greenish [19] with biliverdin. Occasionally the contents are partly watery even after fixation in solution of formaldehyde, but coagulation is usually complete. At times the colloid has been described as resembling cholesterol,[20] and cholesterol crystals have been observed microscopically.[21] The colloid itself is noncharacteristic; occasionally swollen cells are abundantly present within it, and erythrocytes, *Abbauzellen*, leukocytes, gitter cells and desquamated epithelium have been described. The pigment occurring in the colloid and within the epithelial cells lining the cyst reacts with concentrated sulfuric acid [22] to form a deep blue color characteristic of lipochromes. Calcospherites and corpora arenacea have been described in the walls of the cyst but never within the colloid.

There is no a priori reason why the distended, thinned wall of the compressed cyst should not at times show small ischemic necroses and even permit a mechanical discharge of some of its noninspissated content through such minute openings into surrounding cerebrospinal fluid, as do craniopharyngiomas.[23] Such behavior might account for the occasional long clinical remissions [24] and eventually even for the almost cholesteatomatous character that the content assumes on rare occasions.[20]

CLINICAL ASPECTS

Thirty-seven cases of paraphysial tumor had been reported in the literature at the time of publication of Stookey's [21c] paper in 1934, and

18. Hall, A. J.: Two Cases of Colloid Tumor of the Third Ventricle, Causing Death, Lancet **1**:89, 1913.

19. Fulton and Bailey.[3b] Pollock.[16a]

20. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929. (This sketchily described tumor probably is a paraphysial cyst, though it may conceivably be analogous to Dandy's [21a] case 2 of group 2.)

21. (*a*) Dandy, W. E.: Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment, Springfield, Ill., Charles C. Thomas, Publisher, 1933. (*b*) Masson.[2] (*c*) Stookey, B.: Intermittent Obstruction of the Foramen of Monro by Neuro-Epithelial Cysts of the Third Ventricle, Bull. Neurol. Inst. New York **3**:446 (March) 1934.

22. Sjövall.[1] Rinder and Cannon.[14d]

23. McLean, A. J.: Die Craniopharyngealtaschentumoren (Embryologie, Histologie, Diagnose und Therapie), Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:639, 1930.

24. Zimmerman and German.[3c] Byrom and Russell.[14b] Rinder and Cannon.[14d] Josephy.[16b]

since then ten more cases have been recorded.[25] Dandy [21a] in his monograph in 1933 stated that he believed that the only successful removals had been the four he had accomplished (1921, 1929, 1930, 1932), but in that same year German [3c] reported a successful removal accomplished by Harvey in 1931, and Davidoff in discussing Kreschner's [25] paper mentioned four successful removals at the New York Neurological Institute: two by Masson [2] (1932, 1933) and two by Stookey [21c] in 1933.

There have been extended attempts to define a "syndrome of the third ventricle." Academically, of course, this is an absurdity, for a ventricle is an empty space, an absence of substance. Clinically, however, a ventricle possesses size, shape and ostia, defined by a limiting floor, walls and roof. Manifestations of abnormality within the ventricle, therefore, must necessarily be evidenced through its limiting structures, and to attempt to exclude them and their known functions from a consideration of the symptomatology is sheer sophistry. As to what limitation should be fixed for depth of penetration into these structures to define a so-called syndrome of the third ventricle, only pragmatic clinical astuteness in arriving at a localizing diagnosis should warrantably be the arbiter. The thalami, striatum, tegmentum, crura, hypothalamus and quadrigeminal lamina all afford an abundant and rapidly expanding neighborhood symptomatology. When these structures are involved, an adequate interpretation of bilaterality of symptoms and of known function should afford suggestive localization.

A paraphysial cyst practically never attains sufficient size now to disturb constantly more than a small segment of the anterosuperior portion of the third ventricle—a particularly silent region. The one consistent element of the syndrome which it causes is intermittent acute hydrocephalus, due to varying obstruction at the foramina of Monro. Stookey's analysis revealed that in 45 per cent of the cases reported the patient complained of the complete cardinal triad of symptoms indicating intracranial tension and that in 90 per cent at least one of its components was present; in 39 per cent striking instantaneous relief of headache had been obtained by special postures of the head,

25. The tumor reported on by Penfield [20] (the cyst wall was not examined) was obviously a paraphysial cyst; the first of Dandy's [21a] five cases had been reported in 1922 in the periodical literature; Weil (Colloid Cyst of the Third Ventricle, Arch. Neurol. & Psychiat. **28**:726 [Sept.] 1932) and Keschner and Savitsky, writing at a later date (Tumors of the Third Ventricle, ibid. **33**:216 [Jan.] 1935) have reported one case each; Dr. Rinder in a personal communication has told me of an unpublished case of Dr. Simonds, of Chicago; another is mentioned in the discussion of Weil's paper. Two additional cases at the Neurological Institute of New York (not including Stookey's [21c] three) are mentioned by Davidoff in his discussion of Keschner's paper and apparently are those reported by Masson.[2]

probably as a result of the slight gravitational shift of the pendulous tumor away from the foramina. He suggested that fulminating hypersecretory choroidorrhea and acute venostatic edema of the centrum ovale, due to ultimate bilateral obstruction of the lesser veins of Galen by pressure of the finally irreducible impaction within the foramina, might well be the precipitating sequence of the sudden death not infrequently encountered (25 per cent) as a result of such a tumor.[26] His analysis emphasized that in 61 per cent of cases there were some signs of diencephalic localization, while Zimmerman and German and Dandy emphasized that in about 85 per cent of cases there were some ocular signs (diplopia, ptosis, anisocoria); in from 36 to 68 per cent peculiar attacks (often convulsive) with loss of consciousness were noted, while paroxysmal or progressive hemiparesis or hemianesthesia was observed in from a third to a half of the cases.

Statistical analysis, however, is too clumsy a tool to be of more than general value, and individual interpretation of localizing symptoms must finally be given major reliance in making a localizing diagnosis. Ventriculography, probably overemphasized by Dandy,[21a] affords strong collateral confirmation of the bedside diagnosis and in cases of reasonable doubt should always be resorted to before such a serious procedure as transventricular exploration of this region is undertaken. Methods of surgical attack have been so admirably described and illustrated by Dandy [21a] that discussion of this aspect of these tumors would be redundant here.

REPORT OF CASES

I am indebted to Dr. Warren C. Hunter for permission to study and report the following case, well illustrative of the apparent obscurity of symptoms and complaints in the absence of neurologic observation:

CASE 1.—*Paraphysial cyst, headaches, relieved by postural alteration; vomiting; dizziness; sudden death.*

History.—C. T., unmarried, a shipping clerk, aged 23, had always been well, according to his parents, except for moderate constipation. Nine months before his death he had a four day bout of intermittent headaches, so severe that he had to stop work; each individual attack lasted about fifteen minutes, was "like pressure from a cake of ice" and was relieved instantly when he put his head well down between his knees but would return suddenly without warning; lying supine made the headache far worse. He vomited but once, and this was forcibly projectile. He became slightly irritable but returned to work. He once thereafter had a feeling of dizziness at a dance, severe enough to force him to sit down for a while. He had told his parents that he had sharp pains through his head when he attempted to dive.

26. See, however, the article by T. H. B. Bedford (The Great Vein of Galen and the Syndrome of Increased Intracranial Pressure, Brain **57**:1, 1934) for obverse evidence.

On the day of his death he worked as usual but complained in the evening that he had a headache; he ate little supper and went to bed at 7:30 p. m. At 8 he was heard moving about and on inquiry said he "was having one of those spells." His aunt called a physician, but by the time he arrived the headache had stopped. Since the patient complained of constipation a cathartic was recommended. Shortly after the physician had left the headache returned; the patient vomited, collapsed and died in a fraction of an hour. Autopsy was ordered by the coroner and done by Dr. Hunter, pathologist.

Necropsy.—Essentially no abnormality was observed except in the brain, which was fixed by suspension in solution of formaldehyde. The internal table of the skull bore the digitations commonly seen after pronounced intracranial tension, and the sella showed a degree of secondary enlargement. Dr. Hunter reported:

"When removed from the skull, the brain proved to be slightly larger than usual. A single coronal section was made through the unfixed specimen just posterior to the hypophysial stalk; this revealed an immensely hydrocephalic lateral ventricular system, with the ventricular walls thrown into rugous folds; the greatest cross-section diameters of the shrunken fixed ventricles were later found to be 4.5 by 3.5 cm. The septum lucidum, which originally was seen to be an intact thinned turbid membrane, is now fragmented and frayed in the preserved specimen; the corpus callosum has been thinned to a mere lamella, 2.5 mm. thick.

"The primary coronal section has passed through the posterior third of a thin-walled cyst, about 1.5 cm. in diameter, suspended from the roof of the dilated third ventricle immediately between the foramina of Monro (fig. 7). The part of the third ventricle behind the commissura mollis does not apparently participate in the dilatation, although the entrance to the aqueduct of Sylvius is about 3.5 mm. in diameter. The cyst, containing turbid, whitish-brown mucilaginous material, which escaped at the time of the primary section, has been left utterly undisturbed, and a description of its relations and attachments is as follows: the whitish epithelial wall of the cyst is thrown into fine folds; it appears to be possibly from 50 to 75 microns in thickness and can be expanded to a substantially globular form with a diameter of about 15 mm.; it occupies the anterosuperior three-quarters of the dilated third ventricle, its lower part hanging free in the lumen of the ventricle. Its superior portion is attached to the tela choroidea and is lightly adherent anteriorly to the conjoined portion of the fornical pillars, 7 or 8 mm. above the anterior commissure. Laterally, each side of the cyst has apparent anatomic fusion with the anterosuperior border of the foramina of Monro, and indissolubly adherent to its outer surface in this region are the small flocky granulations of the choroid plexus of the third ventricle. These course symmetrically posteriorly over the inferior surface of the cyst as a thin discontinuous series of pinhead-like tufts, to pass upward over its posterior surface and blend with the vascular choroidal attachments 3 or 4 mm. anterior to the posterior commissure underneath the psalterium of the fornices.

"It appears, therefore, that the cyst, probably arising from the paraphysis cerebri, actually presents superiorly and anatomically lies outside the brain, although it hangs pendulous within the third ventricle itself. This leaves the problem as to what membranes, if any, immediately overlie and are adherent to the roof of the cyst between its interfornical attachments. On gross examination the membrane here appears to be considerably thinner than in lower portions of the cyst, but only histologic examination can determine the difference, if any. The outer side of the free superior surface of the cyst is apparently smooth and glistening; anteriorly it strips readily from the fornices, being held by only the most

delicate cobweb-like adhesions; but the posterior part of the superior surface of the cyst has dense areolar adhesions and trabeculae attaching it to the membrane within the meshes of which course the meager choroid plexus and telar vessels of the third ventricle; this attachment lies only 1 mm. or so back of the center of the

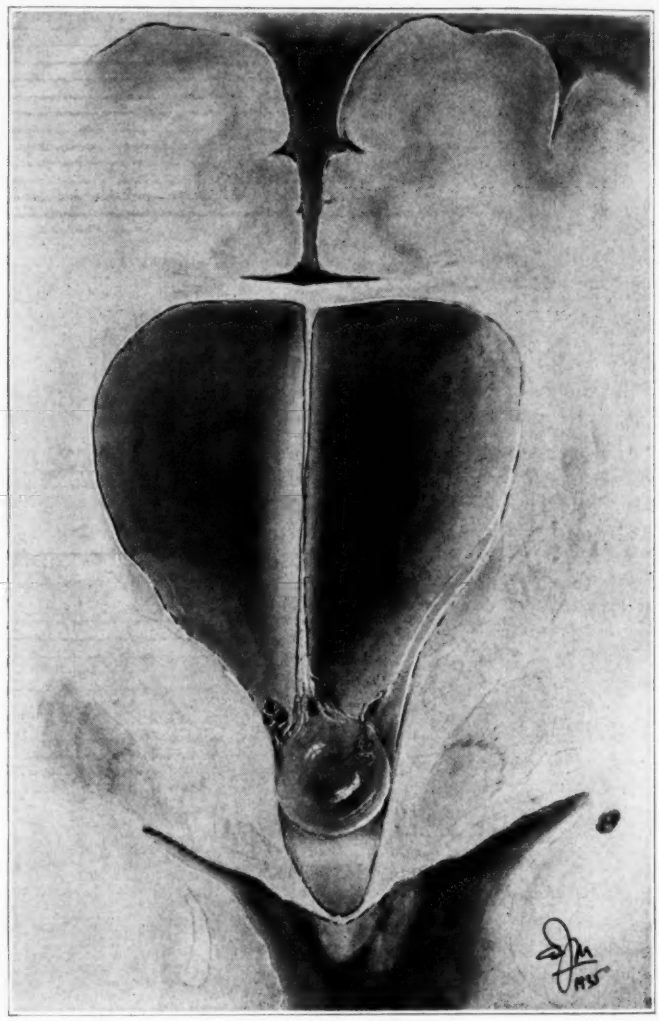

Fig. 7 (case 1).—Drawing of the anterior face of the primary coronal section of the brain passing through the foramina of Monro, disclosing a grapelike paraphysial cyst hanging from the tela underneath the fornices and bearing on its sides tufts of choroid plexus from the roof of the third ventricle.

foramina of Monro." The histologic discussion will be given later (figs. 10 *A* to *F*).

CASE 2.—*Paraphysial cyst, with status dysraphicus: Intermittent internal hydrocephalus, with symptoms of involvement of diencephalomesencephalon (prin-*

cipally of left side); ventriculography; transventricular extirpation; probable transient stenosis of iter; recovery.

History.—B. M. McK., a high school girl aged 16, referred on Feb. 1, 1935, by Dr. Canfield Beattie, complained of headaches, vomiting, diplopia and failing vision. The history of the cardiorespiratory, gastro-intestinal and genito-urinary functions was normal; menstruation had not yet started. Her weight had been constant at 110 pounds (49 Kg.) for several years.

About four months before examination, when the patient had resumed school work in October, she found that the "roofs of her eyes" hurt when she read much and that this was noticeably worse during the afternoon and evening; two months later she began to have transient complete amblyopia during and after sudden changes of posture. For three months before examination she had almost constant aching in the upper part of the right arm and antecubital fossa, particularly when the extremity had been inactive for long. One night early in December she had the first severe attack of headache in the suboccipital region lasting for hours with prolonged vomiting. Afterward she had diplopia on looking toward the right, the degree of separation of images steadily increasing as weeks passed. Subsequent to the headache she had several days of persistent veering toward the right in walking and often bumped into the side of a door and into the wall, both at home and at school, but sustained no falls. For two months she had been subject to more or less constant mild headache but had severe exacerbations on three or four occasions, usually starting around midnight and lasting throughout the entire following day, accompanied by much nausea and repeated vomiting; the pain was at first bilateral and supraciliary but would quickly spread to the right half of the head and thence with increasing intensity to the suboccipital region. The pain was augmented by shaking the head and ameliorated by lying down. During the headaches she had mild distant soughing tinnitus in both ears.

Examination.—The patient was small, plump and well developed, alert and ambidextrous, with a rather wooden facial expression and with some circumoral pallor. She was 4 feet and 11 inches (150 cm.) in height; the temperature was 99.2 F. at 3 p. m.; the pulse rate was 68 and the respiratory rate 14; the skull was 53.5 cm. in circumference, and the head was held tilted slightly downward toward the right shoulder. There was cervicodorsal scoliosis (fifth cervical to fourth dorsal vertebra) with displacement about 2 inches (5 cm.) to the right. The blood pressure was 98 systolic and 62 diastolic. The hands and feet were blotchy and cold. Secondary sexual characteristics were normal.

Neurologic examination showed some concentric contraction of the visual fields, and both blindspots were enlarged to thrice the normal area. Vision in the left eye was 20/25—1; in the right eye, 20/25. The optic fundi showed 1.5 diopters of choked disk on the right and 3.5 diopters on the left, with old exudate over both disks, and with two flame-shaped hemorrhages at the margin of the papilla in the right eye. The pupils were equal in size and reacted normally, but the right one was eccentric medially. There was weakness of the right abducens nerve, and nystagmus was well sustained on looking to the left. The cranial nerves were otherwise normal. Muscular power in the right arm and right leg was slightly diminished; there was mild paresis of the left side of the face of a central type. Pain and temperature perception in the left half of the body were slightly depressed at times, but all other modalities of sensation were normal to objective testing. The tendon reflexes were hypo-active throughout the entire body, and the wrists showed considerable hypotonia; the left patellar reflex was slightly increased over the right one, and there was faint clonus at the left ankle. A positive Rossolimo

sign was elicited on the right side, but no other pathologic reflexes were present. Coordination tests showed both dysmetria and ataxia in the arms, more marked on the left; there was no dysdiadokokinesis; in the Romberg position the patient was unsteady and ultimately fell backward toward the right; she also fell to the right in either tandem or balancing postures; this was found to be more marked in the left leg. No asynkinesia or emotional facial asymmetry was detected on initial examination.

Diagnosis.—The diagnosis was intracranial tumor. The major localizing signs indicated that the tumor was situated in the left mesencephalic region, but the cervicodorsal rachischisis [27] further confused the interpretation of the definite bilaterality of the neurologic findings. Operative intervention was recommended.

Preoperative Course.—The patient entered the Multnomah County Hospital and was again seen in consultation on February 20. She still was dizzy when she first assumed an upright position, but she walked steadily and without a broad base; she had occasional diplopia, but otherwise her condition showed subjective improvement. On reexamination the choked disk measured 2 diopters on the left and 3.5 diopters on the right; the left pupil was 9 mm. in diameter, while the right was only 8 mm. A Rossolimo reflex was occasionally elicitable in the left foot; the tendon reflexes had become hyperactive, but hypotonia was nevertheless still present. There was slight ataxia of the left leg, and dysequilibration was present in special postures, even when the eyes were open; dysdiadokokinesia was not present. There was definite asynkinesia on the right side at times. Cranial roentgenograms did not show elevation of the inion but did demonstrate marked "convolutional atrophy" of the inner table of the skull and congenital deformity of the cervicodorsal portion of the spine (deformed bifid seventh cervical vertebra, abnormal presence of the right half of a bifid eighth cervical vertebra and substantial articulation of the sixth cervical and the first dorsal vertebra on the left side).

The clinical impression recorded at that time was "increased intracranial tension, chronic and acute; in view of the anomaly of the cervical portion of the spine it is possible that incomplete stenosis of the aqueduct or a tumorous congenital cystic lesion may be present. Diffuse chronic intracranial tension often gives false localization to the posterior fossa; it is possible that chronic arachnoiditis may be the only lesion present." In view of the bilaterality of the signs elicitable and the fact that no signs suggestive of strictly intracerebellar involvement could be observed, ventriculograms were recommended to resolve the decision as to the route of exploratory approach (third or fourth ventricle).

Ventriculography (Feb. 25, 1935).—There was no appreciable degree of hydrocephalic atrophy of the subcortex (the ventricle was tapped at a depth of 5 cm.). The initial anteroposterior views (fig. 8 *A*) showed enlargement of the left lateral ventricle: no air had passed into the right lateral ventricle. After considerable gentle manipulation of the head a few cubic centimeters of air entered the lower part of the third ventricle; the anteroposterior views then showed a hemispheric bulge, apparently about 12 mm. in radius, in the lower part of the medial wall of the undisplaced left lateral ventricle, with only a dart of air in the lower portion of the third ventricle (fig. 8 *B*); this, with the complete failure of air to pass into the right lateral ventricle, made the diagnosis of paraphysial cyst evident. Because

27. Ingalls, N. W.: Studies in the Pathology of Development: Some Aspects of Defective Development in the Dorsal Midline, Am. J. Path. **8**:525, 1932. Curtius, I.: Ueber den Status dysraphicus, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:1, 1933.

lateral roentgenograms showed that the air remained throughout only in the inferior part of the entire third ventricle, a superadded cyst of the cavum Vergae was suspected, although the lateral ventricles were not at all widely separated from one another in the anteroposterior views.

Operation.—Left semifrontal osteoplastic bone flap; resection of frontal cortex; transventricular puncture of septum pellucidum; puncture and extirpation of paraphysial cyst.

After pentobarbital sodium had been given orally and anesthesia had been induced by tri-bromethanol in amylene hydrate and local infiltration with procaine hydrochloride, a small left semifrontal osteoplastic flap was elevated, exposing a drumhead tight dura. Ventricular tap released a considerable puff of air, and the dura was then reflected with its hinge toward the eyebrow. Double ligatures were

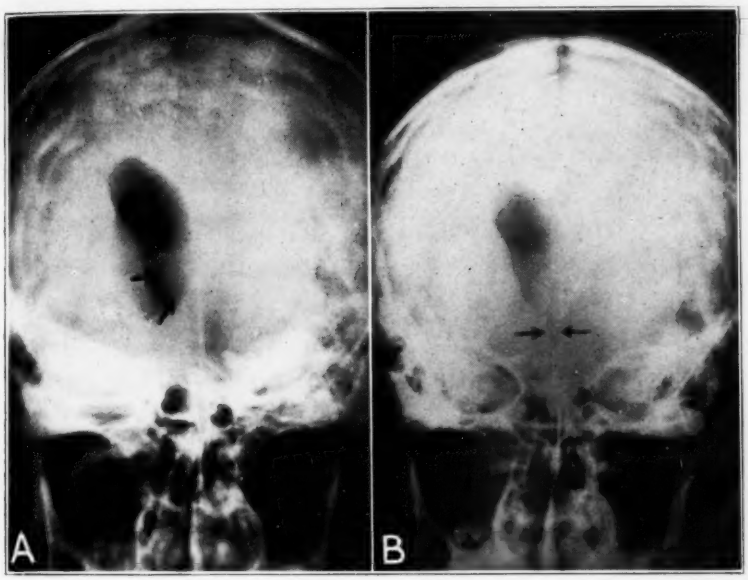

Fig. 8 (case 2).—Anteroposterior roentgenogram showing the hemispheric shadow of the paraphysial cyst impacted in the left foramen of Monro and in *B* the small bubble of air in the undisplaced third ventricle, making unlikely the presence of a glioma or of a cyst of the cavum Vergae.

placed about the cortical vessels at the margins of the exposed field; the cortex was incised electrosurgically, and a wedge-shaped portion 7 by 6 by 4 cm. was resected down to and including the lateral wall of the ventricle. Within the ventricle the choroid plexus could be followed forward to a faint dimple anteriorly, but the actual foramen of Monro was not at that time visualized. The medial wall of the ventricle bulged 10 or 12 mm. into the ventricle, was thinned and had the characteristic bluish color of a cyst. It was incised in two places between veins coursing almost vertically over its surface. A large amount of water-clear fluid escaped. The cavity was at first considered to be a cyst of the cavum Vergae, because of an apparent vascular rete which composed its floor but was ultimately found probably to be the lumen of the right lateral ventricle. When, however,

the lateral wall of the ventricle was further retracted it was observed that there was still present anteriorly a symmetrical bulging into the ventricle, and the operator was perturbed that he could not demonstrate fully the foramen of Monro, although the point of disappearance of the choroid plexus was readily visible. Closer inspection of the bulge disclosed what appeared to be a faintly yellowish band, about 5 or 6 mm. wide, extending upward as a curve anterosuperiorly over its presenting surface, and this was ultimately found to be the flattened pillar of the fornix. The grayish wall was punctured with a myringotome just below the fornical band, and a small amount of thick yellowish stringy mucilaginous material at once escaped and was removed by suction. As the cyst collapsed partially, the dilated foramen of Monro, outlined by the fornix and probably 8 or 10 mm. in diameter, became evident. The wall of the cyst was grasped with pituitary rongeurs and slowly manipulated free; when it was believed the left lateral attachment to the choroid plexus of the third ventricle had been developed, it was obliterated with a silver clip, and the attachment was cut with scissors. A moderate amount of hemorrhage followed, but cotton packing prevented blood from reaching the interior of the third ventricle and the aqueduct. The right lateral attachment was similarly developed, and the cyst was completely removed. Here again moderate but distressing hemorrhage followed, which could be fully controlled only with the electrosurgical coagulation ball. A small amount of clot which had accumulated in the lateral horn of the left ventricle was removed *en masse* by suction. When hemostasis had been made absolute, the field was repeatedly sluiced with warm physiologic solution of sodium chloride, and the wound was closed without drainage. The operation took three and one-fourth hours.

Postoperative Course.—During the latter part of the operation the patient was given 450 cc. of a 5 per cent solution of dextrose by a vein of the leg, and the systolic pressure then rose from 64 to 85 mm. of mercury, where it was maintained by the administration of ephedrine and more dextrose during the next five hours, after which it slowly rose to normal. The pulse rate had remained substantially unaltered at 120 per minute throughout the entire procedure. The patient was conscious, retched repeatedly and responded drowsily to commands but would not talk.

The general condition remained good during the next four days. Fluids were supplied parenterally. The rectal temperature rose slowly to 104 F. as a balloon-like edema of the entire head and face developed. Lumbar punctures yielded increasingly smaller amounts of coral and xanthochromic fluid. The wound healed by first intention; the resection cavity was aspirated several times as the wound was dressed and yielded faintly pinkish cerebrospinal fluid. The edema receded as the temperature fell, and on the sixth postoperative day lumbar puncture again yielded an abundant sustained flow of faintly xanthrochromic fluid. The patient began to talk in short phrases and had spontaneous vertical nystagmus on fixation. There was severe spontaneous coarse resting tremor about the neck and shoulders when she was awake. This tremor was possibly a little more marked on the right side. A billowing overaction of the arrectores pilorum, with shivering, also developed on slightest stimulation. In the following days the "caudate" resting tremor regressed and came to be present only on voluntary motion; by the eighth day it was limited to the right arm, in which, however, marked dysmetria remained, and the grasp was also somewhat weak but without a suggestion of spasticity. By the ninth day speech had returned to normal, the optic disks were flat and the cerebrospinal fluid was still canary colored. The rectal temperature varied from 99 to 101.8 F. However, recent memory was

markedly defective; she forgot that medication had been given, that she had eaten and that her mother had visited her ten minutes before.

During the third week memory improved rapidly and the mental reactions became normal, but when the patient was allowed up in a wheel-chair the temperature again began to fluctuate to 101 F. On the twenty-eighth postoperative day she had a chill, with vomiting, "coryza" and some stiffness of the neck; the temperature rose to 103.8 F. The cerebrospinal fluid was found to be turbid and formed a pellicle, but cultures and bacteriologic smears gave negative results. During the next five weeks such episodes recurred periodically at five or six day intervals, despite the use of hexa-methylene, daily lumbar drainage and a course of inactivated autoserum administered intraspinally. On May 2, because the fever of the most recent episode had lasted for forty hours since the rise three days before, lumbar insufflation of 172 cc. of air was done. Roentgenograms showed only the expected postoperative distortion of the anterior parts of the lateral

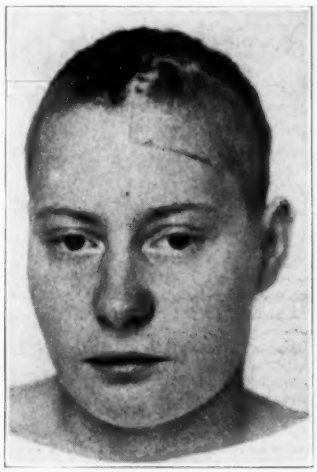

Fig. 9 (case 2).—Photograph of the patient in the third week after operation.

ventricles toward the left, without porencephaly or abnormality of the contour of the third ventricle. The cerebrospinal fluid was substantially normal in response to all laboratory tests. After this treatment the temperature remained normal.

At the time of her discharge, on May 18, the patient still showed mild weakness of the right lower half of the face for voluntary and emotional movements and slight definite atrophy and weakness of the right arm and leg. Fine coordinated movements were well performed. She had a sustained patellar clonus on the right and easily exhaustible ankle clonus on the right. Rossolimo and Hoffman reflexes were consistently present on the right, and there was a fleeting equivocal Babinski response from the outer side of the right sole. The patient showed a slight tendency to veer to the left in walking. Some poverty of speech was noted; she read rapidly and perfectly, repeated all test sentences well and enunciated readily, but spontaneous production of other than simple ideas and short sentences was fumbling. There was no disturbance of superficial sensation. The optic disks were flat, with evidence of mild secondary atrophy.

Subsequent Course (September 1935).—The patient has been participating in normal activities at home. No defect of personality or memory is detectable by the family or her acquaintances. She walks well, has had a vacation at the seashore and has been working in the berry fields with her parents. She sews and cares for her own clothes and plans to finish high school soon. There is still a small degree of motor aphasia. All the reflexes have returned to normal, but she now falls to the left in tandem and balancing postures.

PATHOLOGIC DATA

Histologic Examination.—The stroma of the wall of the cyst in both cases was composed of fibrocollagenous connective tissue in which capillaries were fairly abundant. The lining of the cyst was composed of cylindric and cuboidal ciliated epithelium, which was in a single layer except where cut obliquely. Externally the cyst in case 1 showed nonciliated flattened cuboidal epithelium on its inferior dependent surface; this was not true in the second case. A colloidal content, present in both, was preserved only in case 2.

In case 1 the stroma, which had been fixed in solution of formaldehyde, separated almost spontaneously into two layers (fig. 10 *A*) over much of its extent; across the base of the pedicle of the interchoroidal plexus, however, it was possible to demonstrate only a single thinned sheet. The thickness of the entire wall in case 1 was from 0.2 to 0.5 mm., while in case 2, in which the cyst had been punctured and fixed in Zenker's solution, it was from 0.7 to 1.2 mm. thick. Most of the spindle cells of the stroma lay in a zone comprising the inner four-fifths of the wall's thickness and were intermingled with abundant collagen fibrils (fig. 10 *C*, *E* and *H* and fig. 11 *C* and *D*) which varied considerably in caliber and in degree of fraying; the outer fifth of the stroma was usually (fig. 10 *G* and *H*) almost acellular collagen. Capillaries (collapsed in case 1 and distended in case 2) were never seen in the outer zone of stroma, although rare corpora arenacea were present there in several stages of development in case 2. The interstices of the internal subepithelial stroma in one area of the cyst in case 2 were distended locally with countless swollen cells containing foamy cytoplasm; this area projected as a small macroscopic nodule into the lumen of the cyst (fig. 10 *G*), and the now flattened epithelium over it lost its cilia. Toward the summit of the nodule the epithelium became discontinuous, so that the infiltrating cells desquamated directly into the adjacent colloid (fig. 11, *G* and *H*), while the basal parts of the nodule showed considerable broken-down interstitial blood pigment. The whole process might well represent a stage of abortive repair following an intramural hemorrhage. A few scattered polymorphonuclear and mononuclear cells were seen as small foci elsewhere within the stroma.

The internal epithelial lining of both cysts was composed of ciliated cylindric cells (figs. 10 *D* and *F* and 11 *A* to *E*); cilia were absent only in small areas and only when the layer was distended and the form was flattened. The nuclei were from 7 to 10 microns in diameter, contained a fine linin network with from two to five nucleoli and were bounded by a moderately dense membrane. The nucleus tended to lie at the base of the cell farthest from the free border. The cytoplasm was lacy (fig. 11 *D* and *F*), particularly in the region about the nucleus, and at times the vacuoles became confluent and distended the cell to globular form (fig. 11 *A* and *B*) until it projected partially into the lumen of the cyst, as if about to

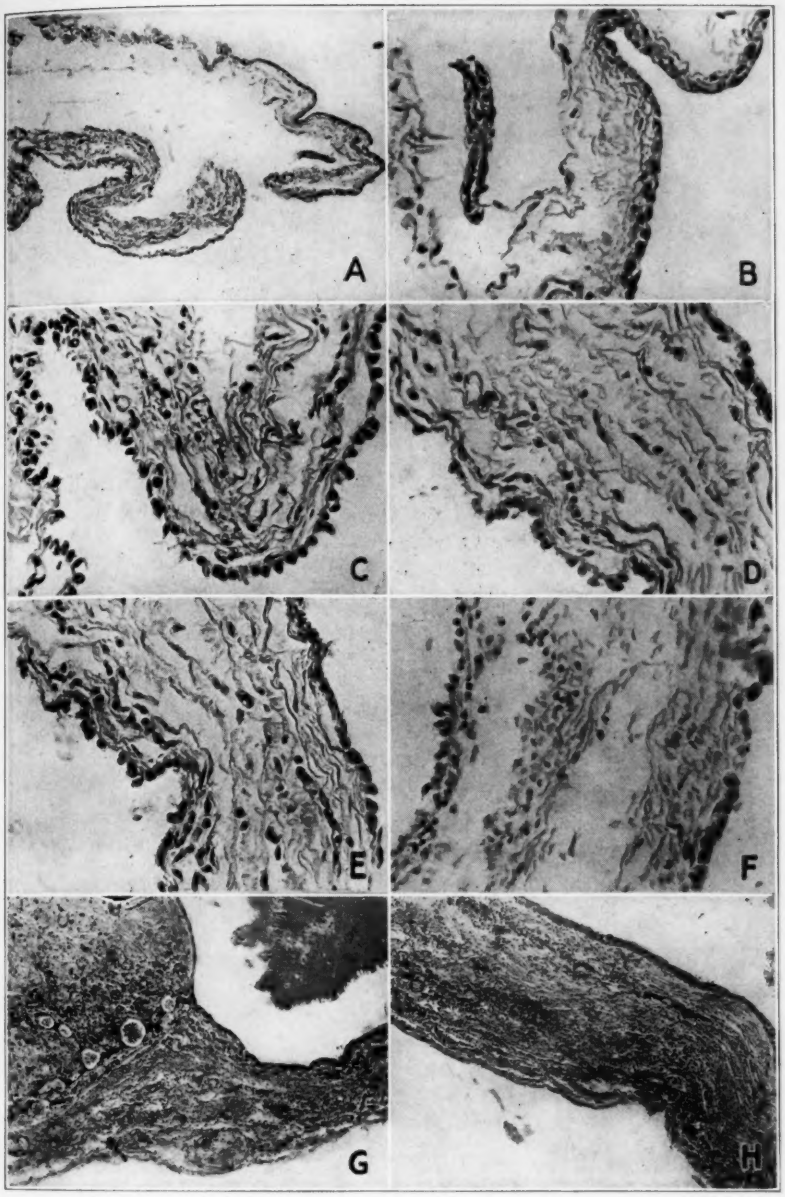

Fig. 10.—Photomicrographs of sections of the walls of paraphysial cysts (*A* to *F*, case 1; *G* and *H*, case 2). *A* (× 30) shows the spontaneous separation into primary and acquired layers, with ciliated paraphysial epithelium toward the lumen inferiorly and an acquired external layer of adult tela (above) bearing flattened epithelium in unabraded portions; *B*, (× 140), flattened nonciliated external epithelium; *C* (× 140), ciliated epithelium presenting toward the lumen of the cyst; *D* to *F* (× 140), fused layers of the complete thickness of the most ventral (dependent) portion of the cyst wall; *G* (× 30), the wall of the paraphysial cyst, showing colloid in the lumen and the edge of the peculiar mural proliferation described in the text (see also figure 11 *G*); *H* (× 30), the usual appearance of the cross-section of the wall, with epithelium only toward the lumen.

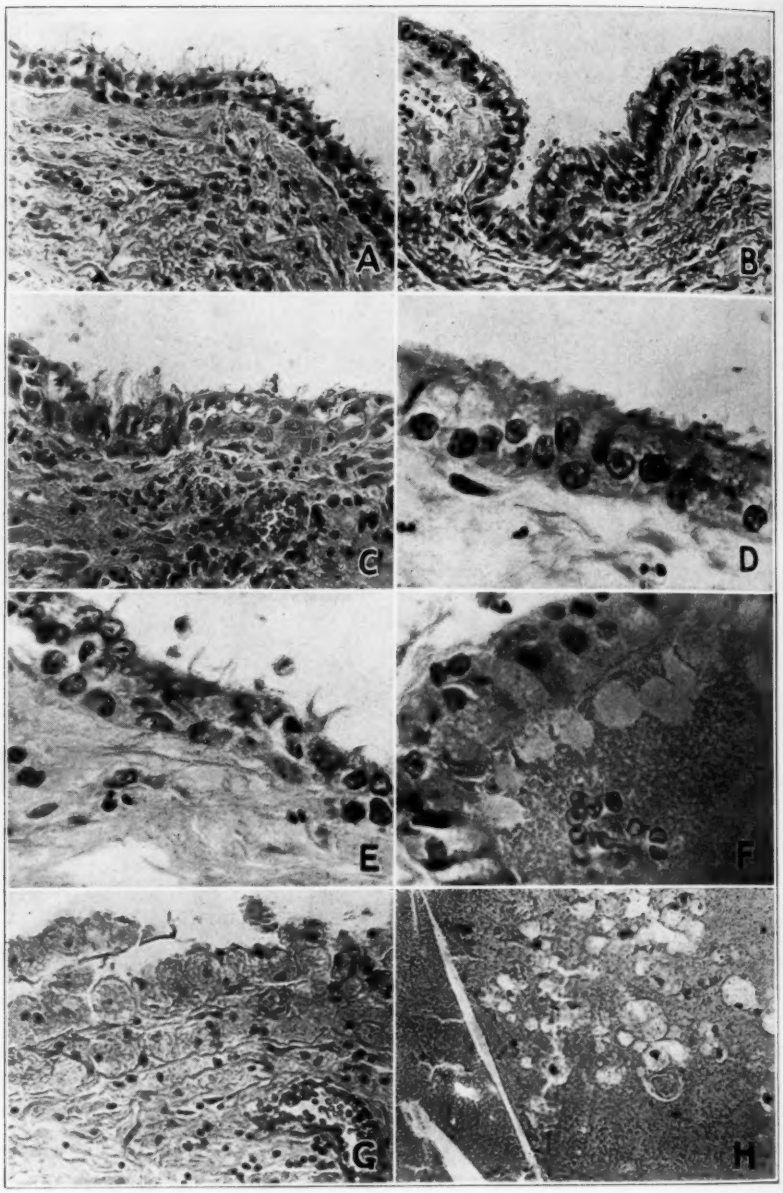

Fig. 11.—Photomicrographs of cross-sections of the wall of the paraphysial cyst in case 2. *A* to *C* (× 140) show the character of the ciliated epithelium lining the lumen of the cyst and of the fibrous stroma derived from the tela comprising the major thickness of the wall; *D* to *F* (× 400), ciliated columnar epithelium with rows of blepharoplasts in *D* and *F* (note the nuclear placement and the lacy perinuclear cytoplasm); *G* (× 140), unepitheliated summit of proliferative mural nodule, showing globular cells with foamy cytoplasm (see also figure 10*G*); *H* (× 140), desquamated and disintegrating foamy cells in the colloid of the cyst.

desquamate. An orderly row of from eight to twenty blepharoplasts was often detected in the cytoplasm, from 3 to 5 microns underneath the ciliated border (fig. 11 *D* and *F*).

The external epithelial layer of the cyst (fig. 10 *A* and *B*), when present, was not in any way different in appearance from the flattened nonciliated cuboidal ependymal lining of the ventricles or the epithelial covering of slightly distended tufts of the choroid plexus of adults (fig. 13 *C*).

The colloid was a homogeneous granular mass which stained faintly pink with eosin (fig. 11 *H*). In it were embedded many scattered naked pyknotic nuclei, rare plasma cells, a few erythrocytes and moderately abundant diffuse clumps of the rounded swollen foamy desquamated cells; the cytoplasm of many of the last-mentioned cells contained an abundance of faintly green refractile globules, while a few carried definite irregular agglomerations of hemosiderin. A few clefts were seen in the colloid (fig. 11 *H*) owing to shrinkage in fixation, but no definite apertures were seen which might be ascribed to the one time presence of cholesterol crystals. Concretions were not present in the material examined.

Lipochrome.—In case 2, when washed frozen sections of the specimen, which had been fixed in Zenker's solution, were blotted on a slide and treated with concentrated sulfuric acid, the colloid at once took on a faint persistent prussian bluish cast by reflected light. While this change was visible macroscopically, it was nevertheless impossible to detect diffuse coloration in the colloid on microscopic examination, but the globular and half-moon forms of pigment described by Sjövall [28] were readily found within the embedded disintegrating cells (fig. 12 *A* and *C*). The cytoplasm of the ciliated cells in these preparations showed over large areas (fig. 12 *B*) a multitude of rounded, facetted-ovoid, dark

28. According to Sjövall,[1] the lipochrome, which he studied at considerable length, is insoluble in formaldehyde, absolute alcohol, ether, chloroform, acetone, benzene, acetic ether or purified petroleum benzine, either at room temperature or in an incubator with from twenty-four to forty-eight hours of immersion. It did not react as a phosphatide with cadmium chloride and was unaffected by osmic acid after months. It stained only faintly with polychrome methylene blue, thionine, neutral red, compound solution of iodine, U. S. P.; stained moderately well with sudan III and better with scarlet red, but not as deeply as do neutral fats, in alcohol-acetone mixture in an incubator. It became an intense blue with concentrated sulfuric acid, best applied as a single drop to a blotted frozen section and the cover glass then immediately added; the coloration lasted for from three to ten hours and then became black and resolved to colorless diffluence. The pigment was in refractile "vacuoles" in the cytoplasm of the epithelial cells of the wall of the cyst as well as in the swollen desquamated cells of the colloid; although it was an anabolic product it assumed half-moon and signet shapes in degenerating desquamated cells and ultimately blended diffusely with the colloid during the completion of cellular disintegration. It differed from the yellow pigment of the choroid plexus in being refractory to osmic acid and differed from ganglion cell pigment in its insolubility in alcohol and ether. See also the section on lipochromes in H. G. Wells' volume entitled "Chemical Pathology" (ed. 4, Philadelphia, W. B. Saunders Company, 1920, p. 478).

blue globules, from 1 to 2 microns in diameter, from twelve to twenty in a cell, and, though occurring fairly uniformly, tended slightly to preponderate toward the base of the cell. In some regions the pigment did not take the characteristic blue coloration; though it appeared morphologically identical, it nevertheless retained the golden or chocolate-brown coloration which it presented in the untreated frozen sections (fig. 12 *C*). A mount of the entire thickness of the filmy inner membrane of the cyst in case 1 when treated with concentrated sulfuric acid also showed occasional isolated cells stuffed with blue pigment, but the globules, though discrete, were considerably smaller than those in case 2. This pigment withstood fixation with Zenker's solution and long storage

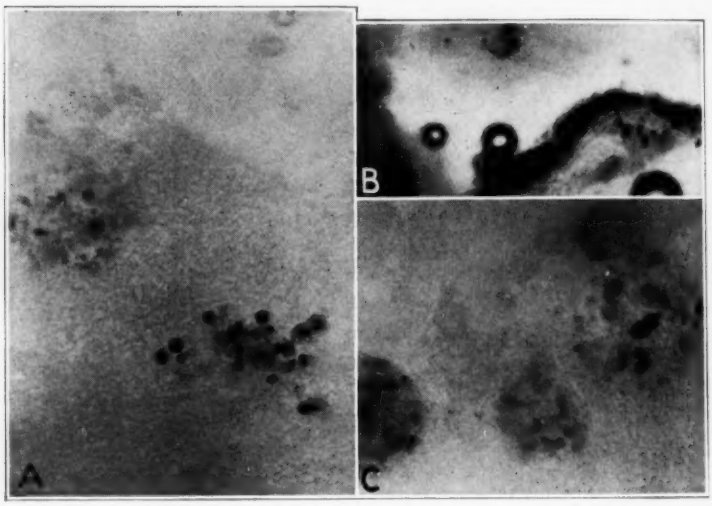

Fig. 12.—Photomicrographs of frozen cross-sections of the paraphysial cyst in case 2, showing the pigmentation. *A* (× 400) shows the blue lipochrome reaction of the pigment in degenerating cells embedded in colloid (note the globular, signet and half-moon forms). *B* (× 100), a cross-section of the cyst wall, shows the pigment, most of which remained deep brown after the application of concentrated sulfuric acid; *C* (× 400), other degenerating cells in the colloid, showing morphologically identical pigment which remained tan to brown and failed to give the blue lipochrome reaction.

in solution of formaldehyde, but it could not be demonstrated in preparations after the tissues had once passed through a xylene-paraffin-balsam treatment.

When frozen midsagittal sections of the roof of the third ventricle of the sturgeon, Acipenser transmontanus, were examined, each cell of the shaggily ciliated ependymal epithelium of the anterior parts of the tela was seen to enclose

from eight to thirty small globular dark brown pigment granules scattered throughout the cytoplasm but tending to aggregate toward the free border of the cell. The pigment was confined to the anterior fifth of the tela and did not extend posteriorly beyond the reaches of a multiple-tubuled structure which burgeoned above the tela in this location and was tentatively identified as the paraphysis; no pigment was seen, however, in the tubules of the mass, except those sparse ameboid chromatophore cells bearing jet-black pigment common to piscine and amphibian arachnoids (these being located in the stroma and not among the epithelial cells). Neither type of pigment changed color when treated with concentrated sulfuric acid. Similar frozen sections of the roof of the third ventricle of Amia demonstrated only sparse ameboid pigment-bearing cells in the stroma and pigmentless ciliated ependymal epithelium. In the many serial sections examined the paraphysis could not be identified; sulfuric acid produced no characteristic change.

When unstained frozen sections of human choroid plexus were examined, very rare areas of groups of epithelial cells bounding the external surfaces of the tufts contained within their cytoplasm mossy and granular coarse aggregations of reddish-brown pigment, ranging from 2 to 4 microns in diameter; the pigment became a translucent reddish-tan when treated with sulfuric acid, and no blue was ever demonstrable.

Frozen sections of the retina of a stillborn babe showed the characteristic polyhedral crystalline fuscin pigment, with from two hundred to six hundred granules to a cell. Although Cajal [29] described a lipochrome pigment as occurring at the base (nonfree border) of these cells, none could be seen in frozen sections, and the lipochrome reaction with sulfuric acid was again negative in my material; occasional greenish-white globules are demonstrable in this location in paraffin sections of the pigment layer of the retina of the guinea-pig, but these, as already explained, could not be made to show a blue lipochrome coloration when treated with sulfuric acid, because of the paraffin-balsam histologic technic used in mounting the sections.

DIFFERENTIAL DIAGNOSIS

1. *Choroid Plexus.*—Any one handling much neuropathologic material soon becomes familiar with the extensive multilocular grapelike cystic degeneration of the lateral choroid plexus which occurs in many conditions, often in elderly persons or in young persons with hydrocephalus. These areas of cystic degeneration may be either solitary or disseminated. Since, however, the choroid plexus is developed as an invagination from the *Adergeflecht* into the lumens of the ventricles, carrying the ependyma before it as a covering, it is obvious that the epithelial layer of the cystic degeneration will be located externally. Moreover, epithelium of the choroidal plexus is not ciliated in man except in the embryonic state, and though it contains abundant mitochondria it does not contain blepharoplasts. Areas of cystic degeneration of the choroid plexus contain only poorly-albuminous fluid, and this is collected in multiple clear confluent microcystic areas, so that the apparent lumens of even individual macroscopic cysts are always spanned

29. Ramón y Cajal, S.: Histologie du système nerveux de l'homme et des vertébrés, Paris, A. Maloine, 1911, vol. 2, p. 303.

by attenuated trabeculae of connective tissue, as shown in figure 13. Cellular débris is practically never seen within them, and calcospherites, both solitary and in aggregations, are practically always present within them in varying amount.

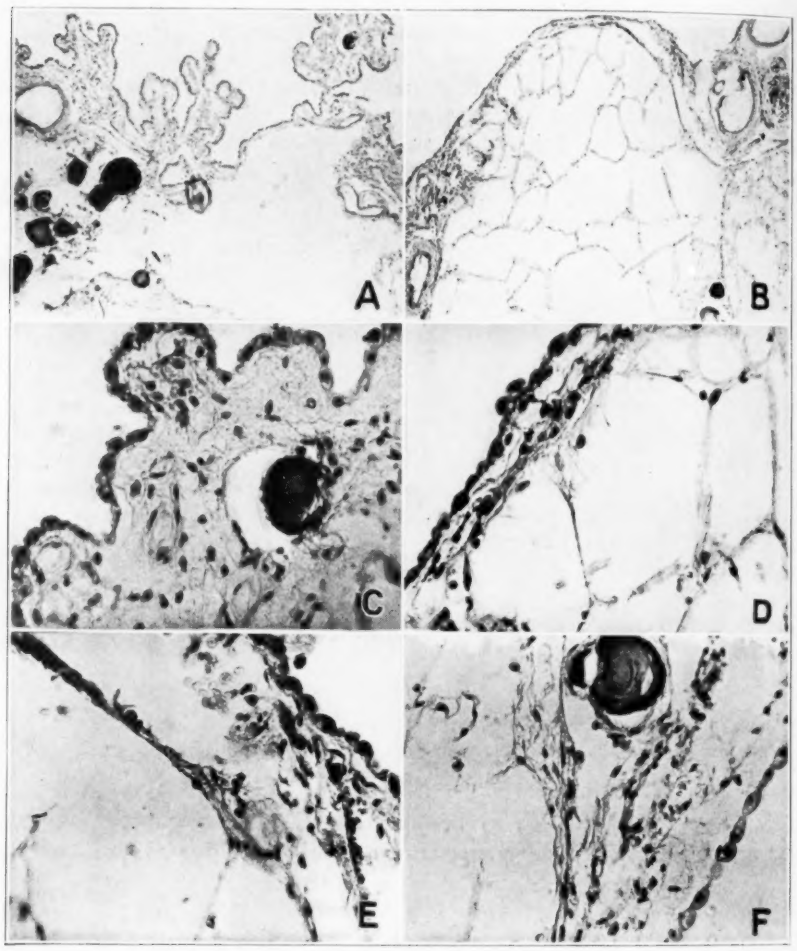

Fig. 13.—Photomicrographs (*A* and *B*, × 30; *C* to *F*, × 140) showing cystic degeneration of the choroid plexus. Note that the epithelium is nonciliated, that it is on the external aspect of the enlargement, that there is no epithelium lining the multilocular cystic cavities and that the cysts are usually spanned by trabeculae of connective tissue. The histologic picture is utterly different from that seen in a paraphysial cyst.

Architecturally, therefore, although a paraphysial cyst has the structure of an occluded *evagination,* a cyst derived from the choroid plexus shows a structure which is typical of a secondary distention of an *invaginated* structure.

2. *Postvelar Tubules.*—Warren [13] has described in the human embryo an abundance of close-set tuftlike simple tubules (which sometimes even form blind cysts or vesicles on stalks) evaginating from the roof plate of the diencephalon just behind the velum transversum;[30] these sometimes project forward the few microns necessary to overlie the paraphysial vesicle (his figs. 18 to 21), which arises anterior to the velum in the telencephalic plate.[31] They may be the homologs of some of the astounding digitations of the dorsal sac, which Edinger [6] described as nearly encircling the brain stem in, for example, Lepidosteus osseus. Although descriptions of their cytology in human beings are not at present available to me, the hypothesis appears reasonable that such postvelar diverticula and vesicles might also form cysts which would be grossly and histologically analogous in every way to those under present examination, that is, unless further investigation can show that lipochrome pigment is not present in the postvelar tubules.

3. *Posterior Evaginations.*—Toward the posterior portion of the roof of the third ventricle the parapineal process [4] evaginates as the probable vestige of the right-sided parietal organ, or "pineal eye." Slightly laterally and posteriorly the vestigial paired racemose precommissural organs [32] are noted, but these, embedded within neural tissue of the epithalamus, could hardly give rise to growths which might be confused with paraphysial cysts, both because of their location and because of their probable histologic composition.

COMMENT

Operative Treatment.—The color of the wall of the cyst as seen at operation in case 2 was practically identical with the adjacent white matter of the brain. It was only by following the choroid plexus forward to its point of disappearance in a flattened dimple that the position of the foramen could be tentatively identified; even then its outline was equivocal until the tumor had been punctured. Such operative adversity has not been previously reported, the cyst customarily being described as a readily visible body, sometimes bluish, greenish, purplish red or yellow-gray. It may be that the operative drawings in the literature are idealized [33] and do not completely represent conditions actually

30. There appears to be no reason based on nonconjectural evidence for homologizing such, and adjacent, structures, with the units of the compound eyes of the next lower phylum, i. e., Arthropoda (Eycleshymer and Davis [8] and Kingsbury [9a]).

31. Johnston, J. B.: The Morphology of the Forebrain Vesicle in Vertebrates, J. Comp. Neurol. **19**:457, 1909.

32. Turkewitsch, N.: Zur Entwicklung des Zwischenhirndaches beim Menschen: "Organon praecommissurale," Anat. Anz. **75**:463, 1933.

33. Dandy.[21a] Masson.[2] Stookey.[21c]

visualized operatively in the depths of the incision, however beautifully they depict anatomic relations. It seems not impossible that a situation and coloration analogous to those in the present case may have been responsible for the unsuccessful outcome reported in German's [3c] second case.

In almost all reported cases of successful extirpation the patient had unexplained fever, with a temperature of from 101 to 103 F, for a period of weeks during convalescence, though otherwise there was no apparent cause for apprehension. This might be ascribed facilely to a regional disturbance of the tuberal nuclei, but it is generally difficult to exclude the possibility of late bleeding in the operative field or even of resolution of a small intraventricular clot which formed at the time of operative removal of the growth. In Davidoff's [21c] case 1, although the removal of the tumor was reported as easily accomplished, the patient nevertheless had persistently bloody cerebrospinal fluid until his death. Intraventricular clots are dangerous not because of the amount of blood lost but because of the danger of occlusion they offer to the foramens and iter; if an intraventricular clot is small enough and is not too firmly lodged, its impaction might be released intermittently (until absorption could take place) by having the patient lie face downward for several periods daily.

In the present operative case the patient showed apparently complete motor aphasia postoperatively for several days, which subsequently completely disappeared, only to recur in slight degree during the period of intermittent hyperpyrexia and to persist mildly to the present. Although none of the excised cortex included any part of Broca's area, it is nevertheless probable that edema within the triangular gyrus, adjacent to the operative field, was the cause of the initial aphasic difficulty. Dandy [21a] has emphasized the obvious necessity for placing the cortical resection far forward, and Masson [2] has utilized only a high slit-like opening in the dura to make an incision across the centrum semiovale to the ventricle. Although this has been successful in Masson's hands, I feel sure that such exposure would have been inadequate for control of the bleeding encountered at the time of extirpation in case 2. It may be stated in passing that the resection of the cortex of the left frontal lobe in this right-handed but ambidextrous girl has resulted in no demonstrable late defect in intellect, character, judgment, memory, orientation, adaptability or personality which has been detectable by parents, friends or attendants or in requested independent psychiatric consultation.

Pathologic Diagnosis.—Except for the practically identical cysts which might arise from the immediately adjacent postvelar tubules, there should remain little possibility of confusion of paraphysial cysts with other neoplasms or degenerations of the region. The histologic picture and the pigmentation are characteristic, and even if the histologic picture

alone for any reason should be insufficient for diagnosis, the chemical reaction of the contained pigment should aid considerably in establishing the histologic identity.

CONCLUSIONS

The paraphysis, which exists in many vertebrates, is present also in human beings in embryonic and at times in postnatal life. Its cystic enlargement forces it to sink through the membranous roof of the third ventricle as a pendulous tumor between the foramina of Monro. Its cytologic picture and pigmentation are characteristic; its identification pathologically is relatively simple. A fairly distinctive clinical syndrome is caused by the tumor, and the condition can be diagnosed with considerable assurance of correctness. The tumor has proved susceptible to successful total extirpation; the tenth case of successful extirpation is recorded.

550 Medical Arts Building.

MULTIPLE TELANGIECTASES OF THE BRAIN

A DISCUSSION OF HEREDITARY FACTORS IN THEIR DEVELOPMENT

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The hereditary nature of certain vascular malformations has been established by the familial occurrence of telangiectasis of the skin and mucous membranes (Rendu [1] and Osler [2]). Such abnormalities tend to be widespread and to occur in particular locations in the affected members of a family. The condition has thus been given various names, such as hereditary epistaxis and hereditary hematuria. In a similar way multiple telangiectatic nodules may occur in the central nervous system and also may be hereditary.

We present the report of a family in which several members in two generations suffered from convulsive seizures. In two members multiple calcified lesions were seen in roentgenograms of the skull. Biopsy of one of the nodules revealed calcified and ossified telangiectasis of the brain.

REPORT OF CASES

CASE 1.—The mother of three of the patients (cases 3, 4 and 5) began to have convulsive seizures at the age of 40. It is said that focal symptoms were present in the left hand. She died of "epilepsy" at 43.

CASE 2.—This patient was a brother of the first patient. All that is known about him is that he had epilepsy.

No other cases of convulsions or other symptoms of disease of the nervous system are known to have occurred in the remaining three members of this generation or in their antecedents, who were apparently healthy Swedish stock.

CASE 3.—Esther M., born in 1900, began to have convulsive attacks several times a year at the age of 8 years. At 14 she awoke one morning with left hemiplegia, from which she completely recovered after four months. Between the ages of 21 and 28 she had no attacks, but thereafter they recurred with increasingly short intervals until June 1928, when she had eighteen major convulsions in two days. Phenobarbital had only a partial effect in controlling the seizures. They

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From the Division of Nervous and Mental Diseases, the Medical School of the University of Minnesota, and the Division of Neurology and Neurosurgery of the University of Chicago.

1. Rendu, M.: Epistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:731-733, 1896.

2. Osler, W.: On a Family Form of Recurring Epistaxis, Associated with Multiple Telangiectases of the Skin and Mucous Membranes, Bull. Johns Hopkins Hosp. **12**:333-337, 1901.

would begin with clonic movements of the left hand and forearm, associated with a peculiar "terrible" feeling in these parts. Soon after this the patient would lose consciousness for several minutes. During the premonitory stage she was usually able to attain a safe position, so that she rarely sustained any injury.

In February 1929 paralysis of the left arm appeared after a convulsion. This gradually improved, and she was fairly well until October 1931, when she began to have epileptic attacks involving either parts of or the entire left side of the body. Left hemiplegia again appeared, remaining complete for two months. During this time the attacks were all partial ones, without loss of consciousness. However, when the patient later recovered the use of the extremities, severe convulsions with loss of consciousness recurred, in addition to frequent mild attacks. She became more inaccessible mentally, volunteering little information. At times

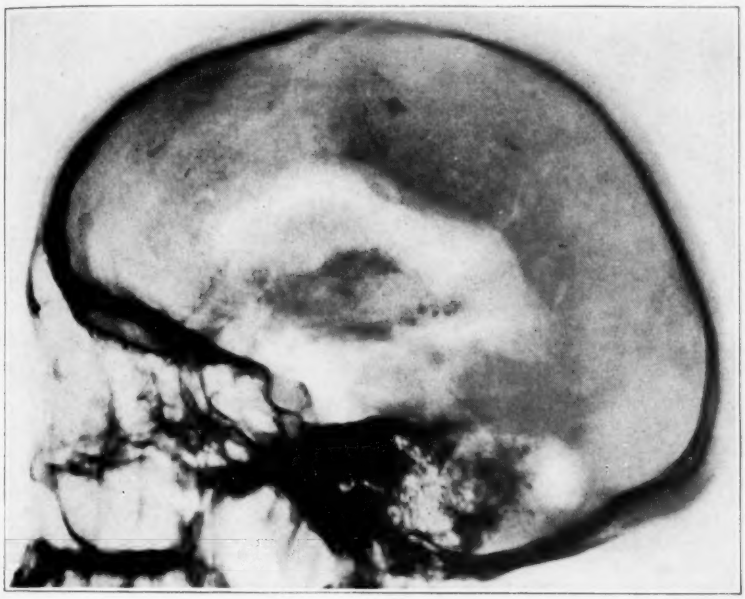

Fig. 1 (case 3).—Encephalogram (slightly retouched) showing moderate ventricular dilatation and areas of intracranial calcification, particularly in the central, temporal and cerebellar regions.

she showed a tendency to poorly controlled laughing or crying. On one occasion a bruit was heard in the right temporal region.

In January 1934 the patient was admitted to the University of Chicago Clinics. A general physical examination revealed no abnormality. There were no cutaneous vascular lesions. Neurologic examination showed spastic paresis on the left side, with exaggerated tendon reflexes, a Babinski sign and moderate atrophy of the muscles of the left arm and leg. The optic disks were normal. There was no alteration of any modality of sensation, and no signs of cerebellar involvement were elicited. The blood and urine were normal. The cerebrospinal fluid contained a moderate increase of protein (85 mg. per hundred cubic centimeters), but otherwise it was normal.

Encephalography (fig. 1) showed that both lateral ventricles were dilated, the right irregularly so, with an abnormal accumulation of air in the right sylvian

region. In addition, there were areas of mottled calcification in the posterior and middle portions of the frontal lobe, the opercular region and the cerebellum, all on the right side. These areas appeared mostly as loose aggregates of granules.

The focal character of the convulsions and the roentgenographic evidence of calcification in the contralateral central region indicated the presence of an irritative lesion of the motor cortex. As hemiparesis was already present, it was decided to attempt extirpation of the lesion.

Operation.—On January 16, exploratory craniotomy in the right central region was performed by Dr. Percival Bailey. The precentral gyrus seemed normal. In the superior temporal convolution a large yellowish-brown area (5 by 2.5 cm.)

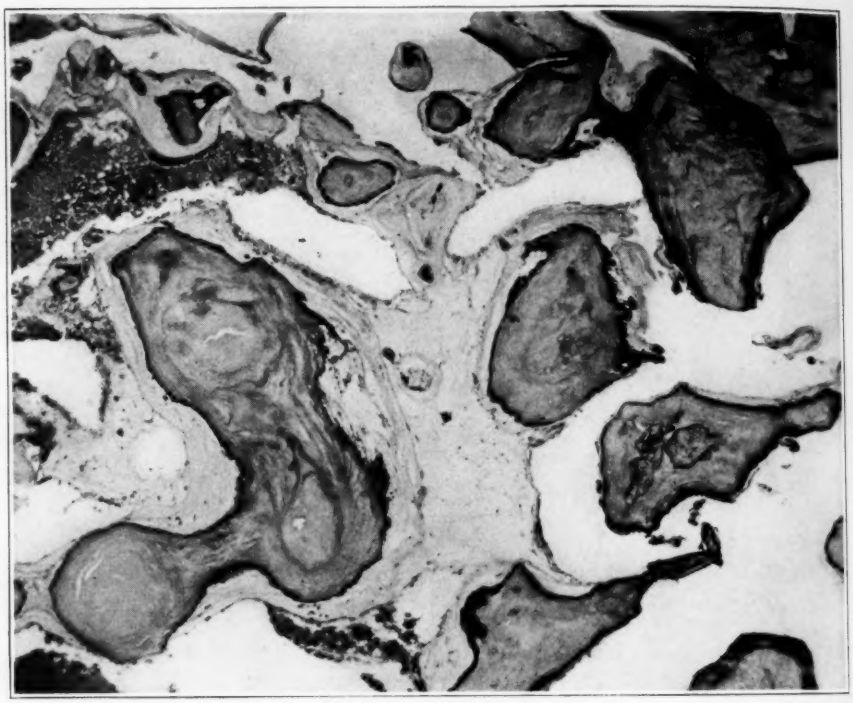

Fig. 2 (case 3).—Tangle of calcified obliterated capillaries. Hematoxylin and eosin stain; × 65.

was seen when the dura mater was reflected. The lesion was not encapsulated. On incision the tissue was tough and calcified. It was not thought advisable to extirpate the lesion, as branches of the middle cerebral artery emerged through it in all directions. Several small bits of tissue were removed for histologic examination. The moderate bleeding was easily stopped with muscle, and the wound was closed.

Course.—The postoperative course was uneventful except for two convulsive seizures the day after the operation and slight drowsiness for a few days. The patient was discharged on January 30 and advised to continue taking phenobarbital (0.06 Gm., three times a day). Since then she has had an occasional major attack but no localized ones, and the power of the left arm has returned.

Pathologic Report.—The pieces of tissue, fixed in a dilute solution of formaldehyde U. S. P. (10 per cent), were decalcified and sectioned in paraffin. The stains employed were hematoxylin and eosin, Mallory's phosphotungstic acid and hematoxylin, Van Gieson's solution of tri-nitrophenol and acid fuchsin, Perdrau's silver impregnation stain and Weigert's resorcinol-fuchsin method. The preparations showed a tangle of freely anastomosing blood vessels of various sizes. Some were capillaries the walls of which had undergone proliferation and calcification, with

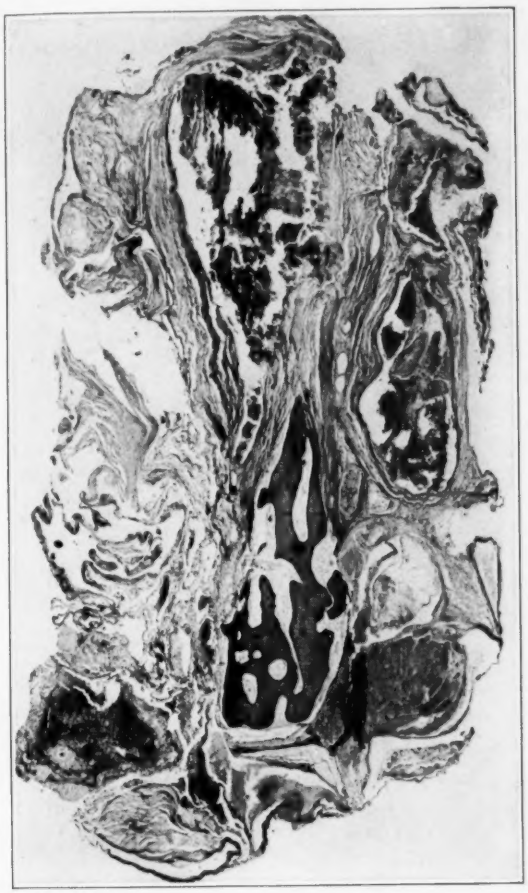

Fig. 3 (case 3).—Another area of the telangiectases, containing huge irregular blood spaces, lined by dense layers of collagen. In the middle is a nodule of bone continuous with collagenous tissue in the upper right margin. Van Gieson's solution of tri-nitrophenol and acid fuchsin; × 22.

obliteration of the lumen (fig. 2). Other vessels were widely dilated and had bizarre shapes (fig. 3). The walls were thickened and consisted mainly of lamellated collagen; they were acellular except for a flattened endothelium. In places a poorly developed elastic membrane was seen, but there were no muscle fibers.

Between the blood vessels was brain tissue which had become densely gliosed, containing numerous large and coarse astrocytes. No hematogenous pigment was to be seen.

Scattered in the tissue were masses of a hyaline substance which evidently had been calcified. After treatment with nitric acid some still stained at the center with hematoxylin. A piece of typical bone was present (fig. 3); this was continuous on one side with collagenous fibrous tissue. Its marrow spaces contained loose reticulin and scattered small mononuclear cells. Loosely applied to the bone were a few giant cells (osteoclasts) containing from eight to twenty-two or more nuclei and finely vacuolated cytoplasm (fig. 4). In one large cell, appear-

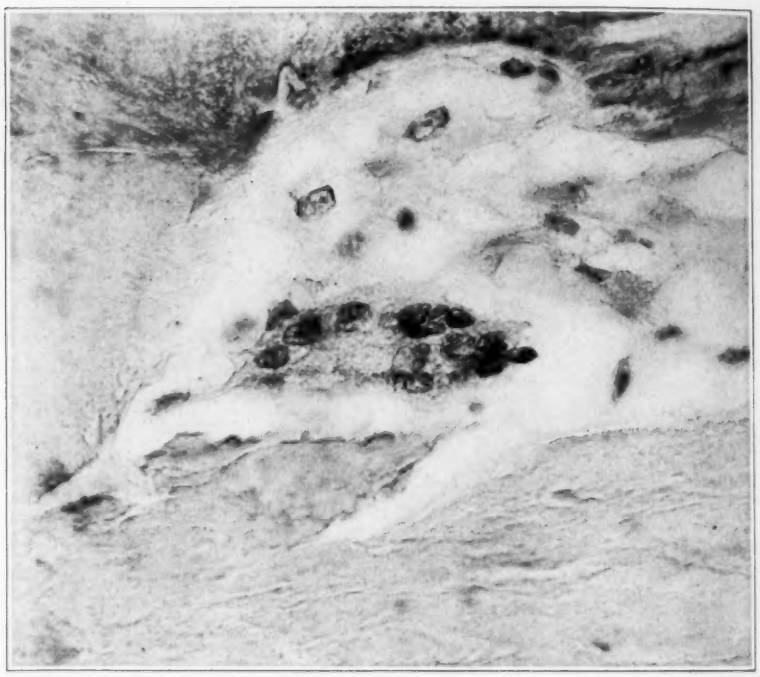

Fig. 4 (case 3).—Marrow space of bone filled with loose fibrous tissue and containing a giant cell (osteoclast). Hematoxylin and eosin; × 600.

ing in at least four serial sections, fifty nuclei could be counted. No layer of osteoblasts was seen.

The diagnosis was cerebral telangiectases with calcification and ossification.

Further Course.—The patient continued to have attacks at long intervals. On April 15, 1936, severe convulsions recurred, and they increased in frequency until they became continuous, involving only the left side of the body. Intensive medical treatment was ineffectual in controlling the seizures, and the patient died on April 19, 1936.

Gross Pathologic Observations.—Complete autopsy was performed five hours later by Dr. A. J. Hertzog, of the department of pathology of the University of Minnesota Medical School. The viscera were normal except for a mild atheromatous change at the root of the aorta. There were no vascular anomalies

aside from those in the brain. The spinal cord was normal. The brain externally showed several hard bluish masses. These varied on section from 1 to 5 cm. in diameter. They were present in the right paracentral lobule, the right superior parietal gyrus, the right superior temporal gyrus and the left hippocampus. In addition, the right cerebellar hemisphere was largely replaced by a hard bluish

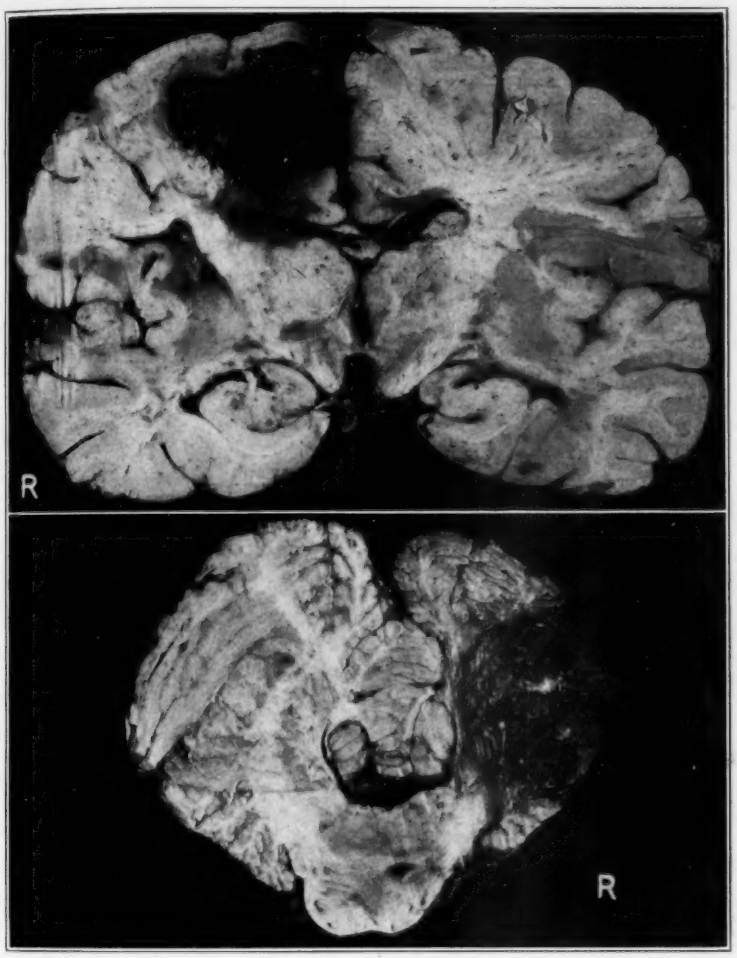

Fig. 5 (case 3).—Photographs of gross sections of the brain, showing multiple telangiectatic nodules in the right cerebral and the right cerebellar hemisphere.

mass of blood vessels containing deposits of calcium (fig. 5). These lesions were all rather sharply demarcated and were composed grossly of a mass of blood vessels. There were no lesions in the brain stem. Coagulated blood was observed in the left lateral ventricle. The vessels at the base of the brain appeared normal.

Microscopic Examination.—The lesions were composed of tangles of widely dilated blood vessels, usually with thickened, fibrous walls. Some of them con-

tained lamellated thrombi. The vessels were usually closely packed together, with little intervascular substance except near the margins of the lesions, where densely gliosed tissue could be seen. Blood pigment was present in abundance about the lesions, mostly within macrophages and in places within hypertrophied astrocytes. Between the vessels there were masses of a hyaline substance, containing in places typical cholesterol clefts. No bone tissue was observed, but there were some deposits of amorphous calcium. The most pronounced calcification was seen in the cerebellar lesion, as might be suspected from the roentgenogram (fig. 1). The hypophysis, which was moderately enlarged and projected upward from the sella turcica, showed microscopically no definite abnormality.

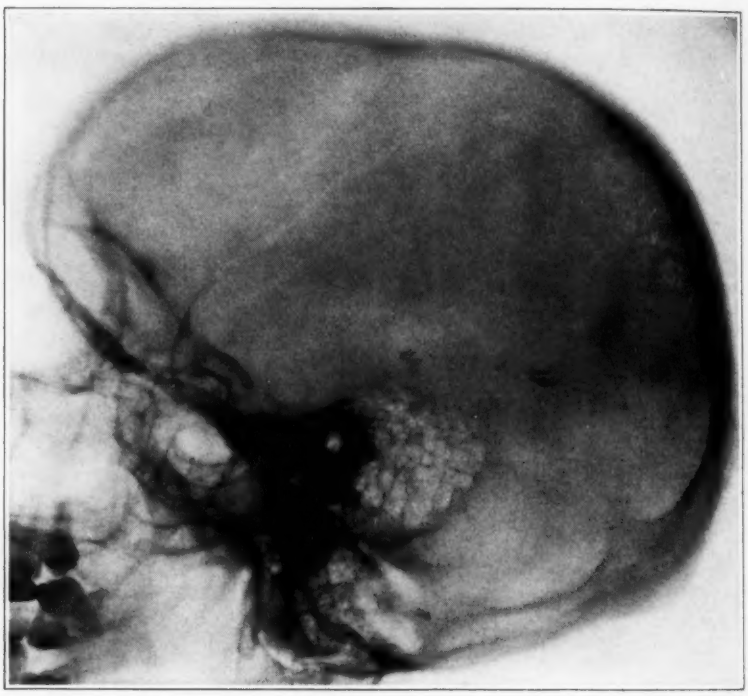

Fig. 6 (case 4).—Roentgenogram of the skull, showing multiple areas of intracranial calcification (particularly in the occipital region).

Case 4.—Anna M., sister of Esther (case 3), was born in 1903. At the ages of 8, 12, 27 and 28 years she had generalized convulsions with loss of consciousness for about two minutes, preceded by a fleeting strange feeling. Since adolescence she had on frequent occasions seen an imaginary "star" to her left. This occasionally was followed by numbness of the left arm, twitching of the left side of the nose and a headache lasting for a half hour. For several years she had also attacks of cramps in the chest and abdomen, accompanied with a feverish sensation, the face feeling warm and the hands perspiring.

Neurologic examination revealed no abnormality. Roentgenograms of the skull (fig. 6) showed several calcified nodules, 3 or 4 mm. in diameter, two or three lying within the right occipital lobe and another in the region of the pineal body.

CASE 5.—Selma M., another sister, was born in 1896. When 12 years of age she began to have attacks of numbness of the left hand or alternately of the left lower part of the face, followed by a generalized headache. These had been less frequent since the age of 18. Neurologic examination revealed no abnormality. Roentgenograms of the skull showed prominent diploic markings in the left parietotemporal region but no intracranial calcification.

Two other siblings are apparently well. No member of this generation has any children.

COMMENT

We are evidently dealing here with a hereditary disease of the nervous system, producing convulsions as its most common symptom. In two members there were attacks closely resembling those of migraine. The pathologic nature was established in one case as telangiectases of the brain.

The condition appears at first sight to resemble the disorder reported by Geyelin and Penfield.[3] These authors described a family in which the father and four children had convulsions, and in each case examination showed multiple calcified lesions of the brain. Operation was performed on one member of the family, and the calcified area was removed. Pathologic study disclosed cerebral degeneration associated with calcification of the arteries of the brain, particularly in the lower cortical laminae. In addition, there was diffuse calcification of the brain substance. The pathologic picture appears thus to be distinct from that of telangiectasis, although a hereditary abnormality of the cerebral vessels may be assumed.

Only a few instances cited in the literature suggest genetic influences in the development of telangiectases of the brain. Kufs [4] reported the case of a man aged 81 with about a dozen small telangiectatic nodules ("cavernomas") in the brain whose daughter was presumed to have pontile telangiectasis. When the daughter was 20 years of age a syndrome suggesting pontile hemorrhage developed suddenly. She was living twenty-five years later, with certain residual neurologic signs, but she had had no recurrence of the acute process.

Oppenheim [5] described a case in which facial nevus and signs indicating a lesion of the opposite (!) cerebral hemisphere were noted, occurring in a family of which another member had epileptic attacks and still another had infantile cerebral palsy. The same author presented also the case of a patient with a pial angioma whose mother had a

3. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy: Endarteritis Calcificans Cerebri, Arch. Neurol. & Psychiat. **21**:1020-1043 (May) 1929.

4. Kufs, H.: Ueber heredofamiliäre Angiomatose des Gehirns und der Retina, ihre Beziehungen zueinander und zur Angiomatose der Haut, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651-686, 1928.

5. Oppenheim, H.: Ueber klinische Eigentümlichkeiten kongenitaler Hirngeschwülste, Neurol. Centralbl. **32**:3-10, 1913.

cavernous angioma of the lip. A vascular nevus of the skin was present likewise in a cousin of the patient, reported on by Fedoroff and Bogorad,[6] who had three cavernomas of the cerebral hemispheres.

A review of the literature reveals reports of fifteen instances of multiple telangiectatic lesions of the central nervous system. The data regarding the lesions in the cases reported by various authors may be briefly noted: Ohlmacher,[7] lesions in the limbic lobe, thalamus and cervical cord; Creite,[8] five lesions in the cerebral hemispheres, several small ones in the cerebellum and another in the pons; Claude and Loyez,[9] lesions in the pons and the cervical portion of the spinal cord and cysts of the frontal lobes; Huebschmann,[10] about thirty small lesions in the cerebral hemispheres, mostly subcortical; Müller,[11] a large number of lesions confined to the cerebral and cerebellar cortex; Fedoroff and Bogorad,[6] the lesions as already noted; Malamud,[12] two diencephalic lesions, one pontile lesion and numerous small lesions in the cerebrum; Berger and Guleke,[13] two lesions in the frontal lobes and a third in the pons; Kufs [4] (previously mentioned), about a dozen nodules in the subcortex, basal nuclei and pons; Sillevis Smitt,[14] two cortical lesions, a third in the globus pallidus and a fourth in the pons; Hosoi,[15] multiple cortical lesions in the right frontal lobe; Russell,[16] a short notice of two cases; Roussy and Oberling,[17] lesions in the pons and cornu ammonis,

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6. Fedoroff, H., and Bogorad, F.: Zur Klinik der Angiome des Grosshirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:497-506, 1925.

7. Ohlmacher, A. P.: Multiple Cavernous Angioma, Fibroendothelioma, Osteoma, and Hematomyelia of the Central Nervous System in a Case of Secondary Epilepsy, J. Nerv. & Ment. Dis. **26**:395-426, 1899.

8. Creite: Zur Pathogenese der Epilepsie (multiple Angiome des Gehirns mit Ossifikation), München. med. Wchnschr. **50**:1767-1770, 1903.

9. Claude, M. H., and Loyez, M.: Sur certaines angiectasies capillaires des centres nerveux, Rev. neurol. **22**:181-187, 1911.

10. Huebschmann: Ueber einige seltene Hirntumoren (multiple Angiome, epithelialer Tumor, Lipom), Deutsche Ztschr. f. Nervenh. **72**:205-224, 1921.

11. Müller, H. H.: Ueber einen unter eigentümlichen Symptomen verlaufenden Fall von multiplen Hirnangiomen, Monatschr. f. Psychiat. u. Neurol. **53**:243-250, 1923.

12. Malamud, W.: Ueber einen Fall von multiplen Hämangiom des Zentralnervensystems mit bemerkenswertem klinischen Verlauf, Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:651-671, 1925.

13. Berger, H., and Guleke: Ueber Hirntumoren und ihre operative Behandlung, Deutsche Ztschr. f. Chir. **203-204**:104-167, 1927.

14. Smitt, W. G. S.: Angiomatosis van het centrale zenuwstelsel, Psychiat. en neurol. bl. **33**:471-480, 1929.

15. Hosoi, K.: Multiple Intracranial Angiomas, Am. J. Path. **6**:235-243, 1930.

16. Russell, Dorothy S., in discussion on symposium on Vascular Tumors of the Brain and Spinal Cord, Proc. Roy. Soc. Med. **24**:363-388, 1930.

17. Roussy, G., and Oberling, C.: Les tumeurs angiomateuses des centres nerveux, Presse méd. **38**:179-185, 1930.

and della Torre,[18] multiple lesions (meningeal ?) of one frontal lobe. Probably to be included is a case referred by Virchow [19] to Hasse and Kölliker, in which telangiectasis of the pons was noted together with scattered foci of dilated capillaries throughout the brain.

In some of these cases vascular anomalies of extraneural tissues have been seen. In the case cited by Virchow there was a "very characteristic telangiectasis" in the liver. Cavernous angiomas of the liver and spleen were present in the case reported by Fedoroff and Bogorad, and in Kufs' case there were multiple angiomas of the liver and vascular nevi of the face and neck. Associated with multiple cavernous angiomas of the brain, Russell observed cysts in the adrenal gland and adjacent kidney and capillary telangiectases of the pelvis of the same kidney; she noted further in a case of solitary cavernoma of the brain a capillary telangiectasis of the skin of the buttock. Jaffé [20] described multiple telangiectases of the skin, bone, thyroid gland, lung and intestines in association with similar lesions of the leptomeninges and of the roots of the spinal nerves. There was a racemose arterial angioma of the pia mater in the case reported by Müller and one of the scalp in the case reported by Fedoroff and Bogorad.

Meningeal tumor may be associated with vascular anomalies, e. g., the solitary parasagittal fibro-endothelioma in Ohlmacher's case and the multiple meningiomas over the cerebral hemisphere affected by the telangiectases in Hosoi's case.

Pathologically the lesions are characterized by fairly well localized tangles of blood vessels. All the nodules in a given case are likely to be histologically similar. The vessels may vary in caliber and in the thickness of their walls. Although they may be as fine as capillaries, they are more frequently dilated, the lesions then being often designated cavernomas. The walls of the vessels vary from simple endothelium with a fine layer of reticulin to dense acellular collagen. The latter type often undergoes calcification. Rarely, true bone formation occurs, as in Creite's case, in a solitary lesion in a patient from the institute of Prof. M. Askanazy, mentioned by Heubschmann [10] and in a case recently reported by Reitano and Loi,[21] in which not only true bone was found

18. della Torre, P. L.: Angiomi venosi multipli del lobo frontale, Riv. di neurol. **6**:167-176, 1933.

19. Virchow, R.: Ueber die Erweiterung kleinerer Gefässe, Virchows Arch. f. path. Anat. **3**:427-462, 1851.

20. Jaffé, R. H.: Multiple Hemangiomas of the Skin and of the Internal Organs, Arch. Path. **7**:44-54 (Jan.) 1929.

21. Reitano, R., and Loi, L.: Focolai osteomielopoietici in una formazione telangectasica del nucleo caudato, Arch. ital. di anat. e istol. pat. **5**:353-370, 1934.

but also myeloid tissue. Oberndorfer [22] described the brain of a girl aged 17, in which he observed four areas of calcification with bone formation. Although he considered the possibility of these being angiomatous lesions, he concluded that they more likely were old softenings. The calcification was present mainly in the walls of blood vessels.

The cavernous type of telangiectasis may usually be recognized as a vascular malformation by the presence of gliosed tissue between the vessels (Cushing and Bailey [23]). At times this tissue may, however, be absent, particularly in the center of a nodule. Such lesions, according to Russell,[16] may be distinguished from the cavernous type of hemangioblastoma by the absence in the telangiectases of intervascular endothelial proliferation. The same method of differentiation appears to apply likewise to the visceral lesions that may be associated with telangiectasis and angiomatosis of the nervous system. In the former the cutaneous and visceral lesions are telangiectatic; in Lindau's disease (angioblastomatosis) cutaneous lesions are exceedingly rare, and the visceral lesions aside from the retinal angiomas are characteristically epithelial cysts of the pancreas and kidney and "hypernephroid" (endothelial?) tumors.[24]

Another important distinction between vascular malformations and hemangioblastomas is the site of predilection of the lesions. A hemangioblastoma occurs most often in the rhombencephalon and in the spinal cord (Lindau [24] and Levin [25]) and is unusual in the cerebrum. Telangiectases, on the other hand, are most frequent in the cerebral hemispheres, although they are not uncommon in the pons, occurring there in approximately half the cases in which there are multiple lesions. The pons is further a favorite site of a single telangiectasis.[23]

An example of pontile telangiectasis, which is of particular interest in the present connection because a hereditary factor may be presumed, has recently been studied at the University of Chicago Clinics.

Case 6.—P. L., a girl aged 8 years, had all her life been prone to vomit when the least excited. Definite symptoms of intracranial disease appeared first on June 1, 1934, when she had a severe headache with vomiting. The following day she felt better, and she remained well until August 26, when the headache and vomiting recurred, the speech became slurred and there was mild diarrhea. She vomited occasionally after this, and on August 31 she had another severe head-

22. Oberndorfer: Verkalkungs- und Verknöcherungsherde im Gehirn, Verhandl. d. deutsch. path. Gesellsch. **15**:316-318, 1912.

23. Cushing, H., and Bailey, P.: Tumors Arising from the Blood-Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

24. Lindau, A.: Studien über Kleinhirncysten—Bau, Pathogenese und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav. (supp.) **1**:1-128, 1926.

25. Levin, P. M.: Multiple Hereditary Hemangioblastomas of the Nervous System, Arch. Neurol. & Psychiat. **36**:384 (Aug.) 1936.

ache, with vertigo and vomiting. Several days later she was examined by a neurologist, who noted paralysis of peripheral type of the left facial nerve, dysarthria, weakness of the left arm, absence of all the reflexes of the left and upper portions of the abdomen and an exaggerated right knee jerk. No Babinski sign or choking of the disk was noted, and the gait was not unsteady. There was some hesitancy in urination. The patient seemed to improve slightly, but on September 6 severe headache and vomiting returned. She was then referred by her physician, Dr. Morley D. McNeal, to the University of Chicago Clinics, where she was admitted that evening.

Examination.—The patient was stuporous. She appeared well nourished. The head was not enlarged and did not yield a cracked pot sound on percussion. Flexion of the head forward was resisted, while retraction caused pain in the frontal region. In general the physical examination revealed no abnormality. Neurologic examination showed that the fundi and visual fields were normal. There was bilateral partial ptosis. Ocular movements were full, with moderately coarse nystagmus in all directions of gaze. The pupils were medium sized and reacted well to light. The corneal reflexes were sluggish on both sides; the muscles of mastication were weak bilaterally, but there was no cutaneous sensory defect. All the muscles of the left side of the face were paralyzed; those on the right were strong. Hearing was good in both ears. The palatal and pharyngeal muscles were paralyzed, and their reflexes were absent. The left trapezius muscle was slightly weak, and the tongue was protruded with difficulty, deviating to the left. All the extremities were weak, the left ones much more than the right. Mild spasticity and moderate ataxia of the left arm and leg were noted. The child stood on a wide base and tended to fall backward. When she walked, however, spasm of the adductor muscles of the legs was evident. There was no defect of any modality of deep or superficial sensation. The reflexes of the arm were equal and normally active; the knee jerks were exaggerated, more on the left, but the ankle jerks were sluggish. There was a bilateral Babinski sign, and the abdominal reflexes were all abolished.

Roentgenograms of the skull were entirely normal, as were reactions to tests of the blood and urine.

Course.—A diagnosis of pontile tumor was made and roentgen therapy was attempted. However, persistent vomiting set in, and the child became more and more stuporous. She was discharged at the parents' request on Sept. 26, 1934, and died at home a week later. Permission was obtained by Dr. McNeal for an examination, which was made three hours post mortem, the body having already been embalmed.

Autopsy.—The cerebral hemispheres appeared normal externally. The leptomeninges were thin, and the cerebral convolutions were well rounded. The cerebellum was well developed, and there was no definite pressure cone. The pons was huge, being symmetrically enlarged (fig. 7). Its external surface was smooth. On midsagittal section the cause of this enlargement of the pons was seen to be a large hematoma (fig. 8), in which three distinct layers of blood could be seen. The ventral layer, the largest, had the appearance of fresh, dark blood; the dorsal one was pale brown and appeared to be the oldest portion of the clot. The tegmentum of the pons was pushed upward, narrowing the fourth ventricle, but the ventricular system was not occluded. Thus, the third ventricle and the cerebral aqueduct were not in the least dilated, and further sectioning of the brain likewise showed the lateral ventricles to be normal. The hematoma was confined to the center of the pons. There was no extension into the adjacent segments of

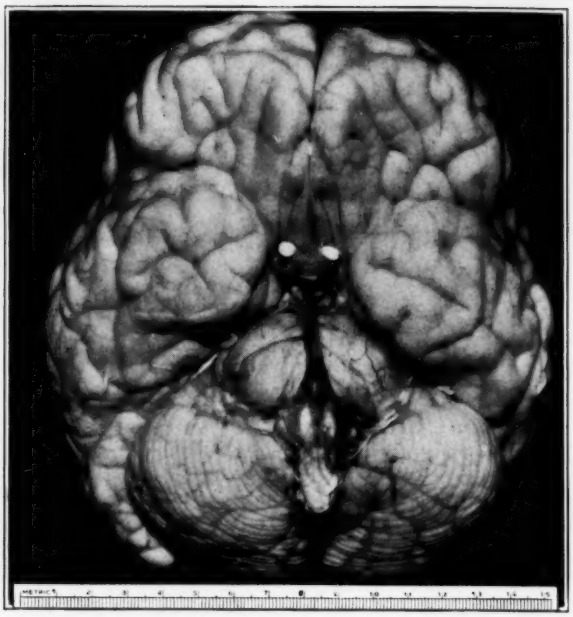

Fig. 7 (case 6).—Inferior view of the brain. Note the enormous pons with a smooth and regular surface.

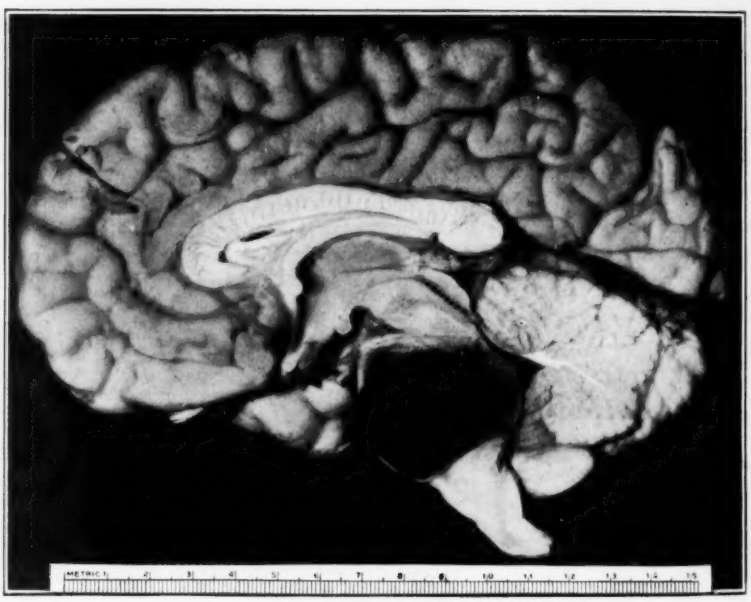

Fig. 8 (case 6).—Midline sagittal view of the brain. The pons is filled with a blood clot which is composed of blood of various ages, as indicated by the lighter color of the dorsal portion. Although the fourth ventricle is compressed, there is no hydrocephalus.

the brain stem, and no rupture into the ventricles or subarachnoid space was noted. The rest of the brain was cut in thin slices, but no other vascular lesions were seen. The spinal cord was not examined.

Sagittal sections through the pons were stained with thionine. These showed that the tissue surrounding the hematoma contained a large number of blood vessels of various sizes (fig. 9). The vessels were larger and more numerous in the dorsal margin. Smaller vessels were scattered in the pons for several millimeters beyond the clot. The walls of the vessels were often composed of a single layer of endothelial cells, but particularly in the larger ones there was moderate adventitial proliferation. In many places there were dense perivascular infiltrations of plasma cells and lymphocytes. The plasma cells were often large and

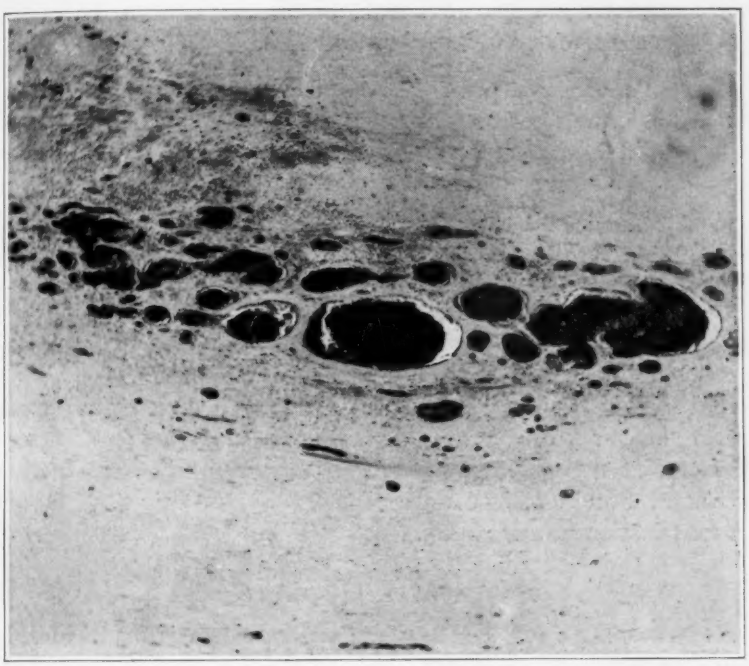

Fig. 9 (case 6).—Section of the wall of the hematoma, showing part of the telangiectases composed of thin-walled vessels of various sizes. The pontile tissue (below) is compressed; the clot (above) is undergoing organization. Note the contrast in the color of the old blood of the clot as compared with the fresh blood in the vessels. Thionine; × 48.

binucleated, the cytoplasm appearing to be finely vacuolated. Although the hematoma was in places sharply demarcated, there was hemorrhagic infiltration of the marginal brain tissue elsewhere, with focal accumulation of macrophages filled with hemosiderin. In some places there were aggregates of round vacuolated cells, which in scarlet red preparations were seen to be filled with neutral fat.

The nerve substance of the pons was markedly compressed, fiber tracts, glia and nerve cells being all directed parallel to the adjacent border of the hematoma. The neurons stained darkly and had an irregular contour and deeply stained

varicose processes. The nucleus in this type of cell was scarcely to be discerned. In other cells the nuclei were irregular in outline but not definitely pyknotic. Nerve cells were seen between the anomalous vessels up to the margin of the clot.

Differences in the blood of various parts of the hematoma were evident microscopically. At the base the red blood cells were fresh and contained normal amounts of hemoglobin. At the vertex, in the tegmentum, they were pale; here the blood was invaded by strands of fibrous tissue and abundant phagocytic cells. A well developed artery was included in the clot.

Histologic preparations were made from many other parts of the brain which appeared in the gross to be at all suspicious of containing a vascular lesion. They were all normal.

Examination of the viscera revealed fatty change and focal necroses of the liver, mild enlargement of the spleen and a few areas of bronchopneumonia. There had been terminal aspiration of gastric contents.

Comment.—Several points in regard to the diagnosis of the condition in this case may be mentioned. Encephalitis had previously been suspected. It is remarkable how often this diagnosis is ventured in children with progressive disorder of the brain stem which may be almost invariably shown to be a glioma (Bailey [26]). So, when this patient was examined a diagnosis of glioma of the pons and medulla was immediately made. In retrospect it seems that the important point which differentiates glioma from the rarer telangiectasis with hemorrhage is the history of repeated sudden attacks in cases of telangiectasis. This might well have been given more attention in making the diagnosis, since the clinical course of glioma of the pons is usually gradual.

The possibility of a hereditary factor was suggested in this case by the fact that the child's grandfather suffered from severe headaches and vomiting and died at the age of 38 from brain tumor. A postmortem examination was not made.

GENERAL COMMENT

The *clinical diagnosis* of cerebral telangiectases is made with difficulty. The presenting symptom is usually epilepsy. Focal attacks and paralysis are frequent. The long duration of symptoms and the absence of intracranial hypertension will exclude neoplasm. Telangiectases may be suspected from the family history, the existence of extraneural vascular malformations or possibly the presence of peculiar areas of intracerebral calcification seen in the roentgenogram. In case 3 such calcification appeared particularly in the form of discrete granules. Other causes of intracranial calcification have been discussed by Courville and Adelstein [27] and need not be enumerated here. Attention is

26. Bailey, P.: Concerning Diffuse Pontine Gliomas in Childhood, Acta neuropath. in honorem L. Puusepp, 1935, pp. 199-214.

27. Courville, C. B., and Adelstein, L. J.: Intracranial Calcifications, With Particular Reference to That Occurring in the Gliomas, Arch. Surg. **21**:801-828 (Nov.) 1930.

called to a report by Fritzsche [28] of a familial disease of the nervous system characterized by diffuse calcification in the gray matter of the brain (cerebral cortex, basal nuclei and dentate nucleus). Although in this family pathologic data are not as yet available, the lesions are probably distinct from those which form the basis of this discussion.

Telangiectases in the pons often produce only such indefinite symptoms as transient attacks of loss of consciousness. Focal symptoms result from hemorrhage. It is suggested that this type of expanding lesion may be clinically differentiated from neoplasm by the occurrence in patients with telangiectases of acute increases of symptoms.

SUMMARY

Telangiectasis of the brain may be multiple and hereditary, just as it may be in other organs of the body, notably in Rendu-Osler's disease.

A report of a family is presented in which five members suffered from convulsive seizures or migrainoid attacks with focal manifestations. Roentgenograms of the skull in two cases disclosed multiple areas of intracranial calcification. Pathologic examination of the lesions in one case showed them to be telangiectases of the brain.

Reports of other cases of multiple telangiectases of the nervous system are reviewed.

The lesions vary from case to case in histologic detail but all the lesions in each case tend to be similar.

A case of single telangiectasis of the pons with hemorrhage is presented. In this case a pontile syndrome had developed by a series of acute episodes.

The clinical diagnosis of telangiectasis of the brain is difficult. Grounds on which such a diagnosis may be made are discussed.

28. Fritzsche, R.: Eine familiär auftretende Form von Oligophrenie mit röntgenologisch nachweisbaren symmetrischen Kalkablagerungen im Gehirn, besonders in den Stammganglien, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:1-29, 1935.

THE PYRAMIDAL TRACTS

AN EXPERIMENTAL STUDY OF THE CORTICOSPINAL AND OTHER COMPONENTS IN THE RABBIT

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CHICAGO

Knowledge of the pyramidal system is incomplete and confused because too much reliance has been placed on study of normal histologic material rather than on critical experimental methods. This is especially true of the rabbit. According to Linowiecki,[1] the pyramidal tract of the rabbit is located in the lateral funiculus of the spinal cord. His conclusion was based on work of Lenhossék,[2] Bechterew [3] and Münzer and Wiener [4] and was strengthened not by experiments but by his own study of normal material. Lenhossék's and Bechterew's sections stained with the Weigert method from normal new-born rabbits exhibited an area in the dorsal part of the lateral funiculus from which myelin was absent, and the authors assumed this area to be in the position of the corticospinal tract.

Münzer and Wiener employed both normal histologic preparations and degenerating postoperative material stained by the Marchi technic. On the basis of their experimental studies they stated that few pyramidal tract fibers continue into the spinal cord of the rabbit. They expressed the belief that the pyramidal system contains corticospinal, rubrospinal and other subcortical neurons in every animal, that the corticospinal fibers are the principal components in higher forms (dog) and that rubrospinal and subcortical fibers are predominant in lower animals (rabbit). Van der Vloet [5] likewise employed the experimental method. He found the pyramidal tract completely crossed in the lateral

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From the Department of Anatomy, Northwestern University Medical School.

1. Linowiecki, A. J.: The Comparative Anatomy of the Pyramidal Tract, J. Comp. Neurol. **24**:509, 1914.

2. Lenhossék, M.: Ueber die Pyramidenbahnen im Rückenmarke einiger Säugetiere, Anat. Anz. **4**:208, 1889.

3. Bechterew, W.: Ueber die verschiedenen Lagen und Dimensionen der Pyramidenbahnen beim Menschen und den Thieren und über das Vorkommen von Fasern in denselben welche sich durch eine frühere Entwickelung auszeichnen, Neurol. Centralbl. **9**:738, 1890.

4. Münzer, E., and Wiener, H.: Das Zwischen- und Mittelhirn des Kaninchens und die Beziehungen dieser Teile zum übrigen Centralnervensystem, Monatschr. f. Psychiat. u. Neurol. **12**:241, 1902.

5. Van der Vloet: Ueber den Verlauf der Pyramidenbahn bei niederen Säugetieren, Anat. Anz. **29**:113, 1906.

funiculus but did not describe its course through the spinal cord; probably he made no observations of its lower part. Simpson [6] found the decussation incomplete and reported having observed a few fibers in the lateral funiculus of the same side. It is uncertain whether he traced the course farther; however, he did say that the pyramidal tracts in the rabbit are similar to those in the cat, dog and monkey, but that fibers are fewer. Brouwer [7] noted that corticospinal fibers terminate in the reticular formation of the cervical portion of the spinal cord of the rabbit ventral to the substantia gelatinosa, but he did not elaborate on this observation.

Results of cortical stimulation in the rabbit are discordant. Ferrier [8] localized cortical areas for the face, forelimbs and hindlimbs, but Mills [9] stated positively that a hindlimb area does not exist. Allen [10] and Laughton [11] were unable to find a hindlimb area. Laughton described flexion of the shoulder and elbow occurring commonly, but he stated that flexion of the wrist occurs infrequently. He observed extensor rigidity and found paresis persisting for a number of days after decortication.

The present study was undertaken in an attempt to settle some of the differences of opinion regarding the pyramidal system of the rabbit. It was hoped that a careful investigation of corticifugal neurons in a mammal with relatively simple cortex might lead to a better understanding of such pathways in man.

MATERIAL AND METHODS

Chinchilla, albino and plymouth giant rabbits of both sexes and of various ages and sizes were used. The cerebral cortex was explored, and lesions were placed

6. Simpson, S.: The Motor Areas and Pyramid Tract in the Canadian Porcupine, Quart. J. Exper. Physiol. **8**:79, 1915.

7. Brouwer, B.: Centrifugal Influence on Centripetal Systems in the Brain, Arch. Neurol. & Psychiat. **30**:456 (Aug.) 1933.

8. Ferrier, D.: The Functions of the Brain, London, Smith, Elder and Co., 1886.

9. Mills, W.: I. The Functional Development of the Cerebral Cortex in Different Groups of Animals; II. The Psychic Development of Young Animals and Its Physical (Somatic) Correlation with Special Reference to the Brain; III. Cortical Cerebral Localization with Special Reference to Rodents and Birds, Tr. Roy. Soc. Canada **2**:3, 1896.

10. Allen, W. F.: Location in the Spinal Cord of Pathways Which Conduct Impulses from the Cerebrum and Superior Colliculus, Affecting Respiration, J. Comp. Neurol. **43**:451, 1927. Allen stated that two of his students had followed the corticospinal tracts into the spinal cord of the rabbit. Private communication with Dr. Allen revealed that some error in publication of the article had occurred; the work to which he referred was done on the cat and not on the rabbit.

11. Laughton, N. B.: Studies on the Occurrence of Extensor Rigidity in Mammals as a Result of Cortical Injury, Am. J. Physiol. **85**:78, 1928.

in the cortex, basal ganglia or spinal cord, the animals being anesthetized with pentobarbital sodium administered intravenously or intraperitoneally.

Series 1.—Twenty-one rabbits were decorticated with a sharp scalpel; an attempt, not always successful, was made to avoid damaging the underlying basal ganglia. After from seven to twelve days representative pieces were taken from the lesion, the brain stem and the spinal cord. Tissue from five rabbits was fixed in Müller's fluid for fourteen days and then treated with Marchi's stain; that from five of the animals was fixed in a dilute solution of formaldehyde U.S.P. (1:10) and then placed in Müller's fluid for fourteen days before being treated with Marchi's stain, and that from five others was fixed in formaldehyde and then placed directly in a modified Marchi solution.[12] Two rabbits were allowed to live for three months. Sections removed from the cerebrum, brain stem and spinal cord were stained by the Weil method for myelin sheaths and the Davenport silver method for axis-cylinders.

Series 2.—Removal of the cortex along the rhinal fissure was attempted in the remaining four animals. Material from various parts of the brain and spinal cord was prepared by the modified Marchi method.

Control Series.—Six cats were subjected to removal of the motor cortex; fourteen days was allowed for degeneration. The tissue from two of the animals was treated by each of the Marchi procedures. Material from two cats which had been allowed to live for three months was stained by the Weil and Davenport methods.

Series 3.—Lesions were placed in the basal ganglia of fourteen rabbits. In fourteen days were allowed for degeneration. The tissue from two of the animals and the tissue was stained by the modified Marchi technic. The remaining rabbit was killed after three months, and the brain and spinal cord were stained by the Weil and Davenport procedures.

Series 4.—In a group of five rabbits hemisections of the spinal cord were made at the level of the fourth cervical, fifth cervical, seventh cervical, fifth dorsal and seventh dorsal vertebrae. Tissue from the lesions was stained with hematoxylin and eosin, and the portions of the spinal cord caudal to the lesions were prepared by the modified Marchi method.

Series 5.—Preliminary to stimulation experiments, dial[13] or pentobarbital sodium was given intraperitoneally; this was supplemented by ether to prevent the animals from regaining consciousness. The cerebral cortex was explored electrically. A Dubois-Reymond inductorium with two dry cells in the primary circuit furnished the current supplied with bipolar electrodes the points of which were spaced 0.5 mm. and 1.5 mm. apart; the latter proved to be the more useful separation. The coil was set at from 7 to 10 cm., depending on the irritability of the cortex and the centers stimulated. The need for such strong current is probably explainable on the basis of poor development of the corticospinal pathway in the rabbit. Care was exercised to keep the cortex dry while it was being stimulated and to avoid deep narcosis. At the conclusion of each experiment the cortex was carefully scraped away on one side with a sharp scalpel. Ten days later the

12. Marchi's solution plus a 2 per cent solution of acetic acid appeared to give the most reliable results; it was employed in all the remaining experiments on rabbits (Swank, R. L., and Davenport, H. A.: Marchi's Staining Method: Studies of Some of the Underlying Mechanisms Involved, Stain Technology **9**:11, 1934).

13. A solution of Dial-Ciba was obtained from the Ciba Company, Inc., New York City.

intact part of the cortex and the area from which the cortex had been removed were again stimulated. After this the brain was excised and fixed in formaldehyde in order that the exact extent of the lesion might be determined. Postoperative observations of posture and behavioral reactions were made on all animals, including those used for the degeneration studies.

ANATOMIC OBSERVATIONS

A study of the cerebral cortex and basal ganglia in a series of sections of the normal rabbit brain stained by the Weil technic shows the lentiform nucleus to be well developed and to extend from well back in the occipital to the anterior part of the frontal lobe. Its anterior end lies just under the cortex. Consequently it is difficult to avoid damaging this nucleus in operations on the cortex, and unless the lesion is studied histologically no accurate estimation of the extent of damage is possible. Cauterization of the cortex should be condemned unless the most rigid control by postmortem histologic study is carried out. Several of my

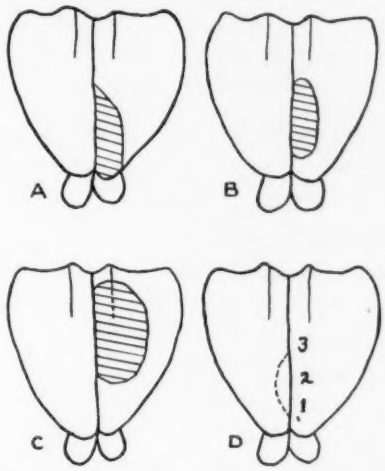

Fig. 1.—*A, B* and *C,* dorsal views of brains of rabbits showing areas of cortex removed in three experiments. *D,* dorsal view of the brain of a rabbit in which the area outlined by a broken line represents the precentral motor area as shown by Winkler and Potter (An Anatomic Guide to Experimental Researches on the Rabbit's Brain, Amsterdam, W. Versluys, 1911). The numbers on the opposite hemisphere indicate points stimulated to obtain movements of (*1*) the face and jaws, (*2*) the head and neck and (*3*) the scapula.

attempts to remove the cortex alone resulted in marked lesions of the anterior part of the lentiform nucleus. There is reason to suspect that other investigators have overlooked injury of the lentiform nucleus in decorticating rabbits.

Results of Decortication.—Figure 1 *A, B* and *C* show the regions removed from the brains of three rabbits in series 1; the diagrams are typical of the picture in twelve of the decorticated animals from which cortex only was removed. Because the degeneration was similar in twelve specimens results can be summarized in one description.

Marchi preparations of the mesencephalon showed a few scattered small globules of lipoid in the homolateral peduncle. In the pons the area occupied

by the pyramidal tract[14] was greatly reduced in size; the particles of lipoid were so few and so evenly scattered that one might conclude both tracts to be normal at first glance. In the medulla oblongata, the degenerating globules occupied a comma-shaped region (fig. 2*F*). The decussation of the pyramids consisted of small interdigitating fascicles, not like those in the cat. Most degenerating fibers crossed. In the spinal cord they deployed in the well developed reticular formation of the first cervical segment. A few formed a small group adjacent to the gray column ventral to the substantia gelantinosa, but none was to be seen below the lower part of the first cervical segment. A few uncrossed fibers ended in the reticular formation.

Study of sections stained by the Davenport silver method revealed clearly a marked but incomplete loss of axis-cylinders not accounted for in the Marchi preparations (fig. 2 *C* and *D*). No evidence of degeneration was found below the first cervical segment.

Several attempts to remove the narrow strip of cortex adjacent to the rhinal fissure (series 2) furnished little additional information. There the cortex overlay the lentiform nucleus and was so thin that tissue reaction resulted from the operation and the necrosis extended some distance into the nucleus. The resulting degeneration in the brain stem and spinal cord resembled that following operations on the lentiform nucleus.

Results of Lesions of the Basal Ganglia.—The mortor cortex and caudate nucleus exclusive of other basal ganglia were damaged in three rabbits. Degeneration in the brain stem and spinal cord was essentially like that following simple cortical injuries.

Eleven animals of series 3 suffered considerable damage of the lentiform nucleus or of the lentiform nucelus and motor cortex. Marchi preparations showed greater numbers of degenerating sheaths than after lesions of the cortex alone (fig. 2*G*). Destruction of the middle and caudal thirds of the nucleus resulted in marked degeneration. Many globules of black lipoid appeared in the midbrain, pons and medulla oblongata; the pyramids seemed to be filled with them. Many of the degenerating sheaths were larger than those seen after simple cortical lesions, but, in contrast with the observations on the cat (fig. 2*H*), they were small. Below the pons a conspicuous crossing of fibers for the opposite reticular formation occurred, after which the size of the pyramids was reduced to a remarkable degree. The degenerating fibers could be followed through the decussation of the pyramids to the spinal cord. They became scattered throughout the reticular formation at the lower end of the medulla oblongata and the first cervical segment of the spinal cord, where many ended. Some continued in distinct bundles next to the dorsal gray column. At the second and third segments the tract occupied the same position but was greatly reduced in size. Few fibers could be seen at the fifth segment, and none was present at the seventh. A homolateral tract was not evident below the first.

One specimen stained by the Weil and Davenport methods was found to have a lesion involving the cortex and almost the entire lentiform nucleus. Silver-stained sections revealed absence of axis-cylinders in the pyramids (fig. 2*E*).

Results of Lesions of the Spinal Cord.—The fourth series of experiments was devised to determine the presence or absence of spinal cord tracts taking origin in the cervical region. Results of hemisection at the fourth and fifth cervical verte-

14. The term "pyramidal tract" is used here to designate all fibers coursing in the cerebral peduncles and pyramids regardless of whether their origin is cortical or subcortical.

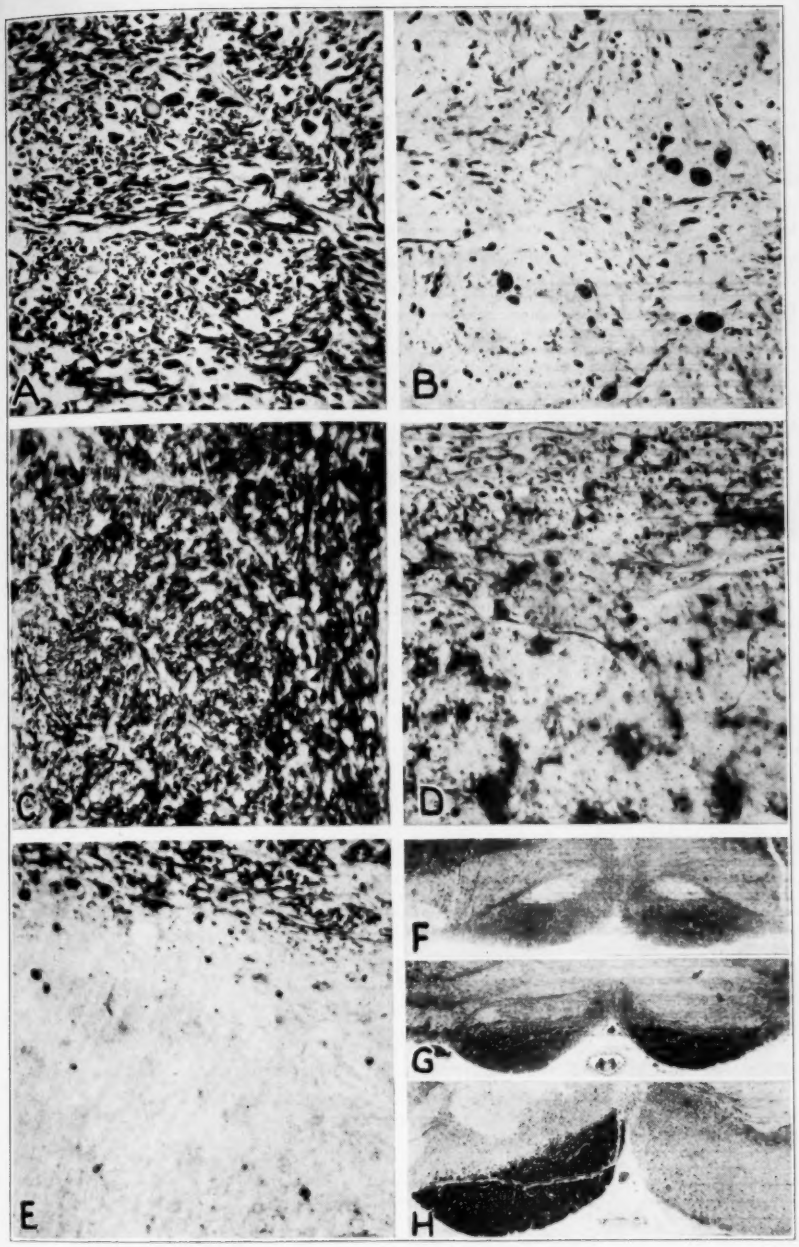

Fig. 2.—*A*, *B*, *C* and *D*, photomicrographs of sections stained by Davenport's technic (× 360). *A*, area in the center of a normal pyramid of the cat. *B*, area in the center of the pyramid of a cat after simple cortical extirpation. A few normal axis-cylinders are present. *C*, area in the center of a normal pyramid in the rabbit. *D*, area from the center of the pyramid of a rabbit after simple cortical extirpation. Large number of normal axis-cylinders are present. *E*, area in the pyramid of a rabbit after destruction of both the cortical and the lentiform nucleus. The section borders the dorsal portion of the pyramid; in the upper part a small piece of the normal brain stem is included for comparison. There is absence of axis-cylinders in the lower, degenerated portion of the section. *F*, *G* and *H*, photomicrographs of sections stained by the modified Marchi procedure (× 10). *F*, pyramids of a rabbit after simple destruction of the cortex. The right pyramid contains a few small scattered degenerating fibers which are demonstrable at this magnification. *G*, pyramids of a rabbit after destruction of the cortex and lentiform nucleus. There is marked degeneration in the right pyramid. *H*, pyramids of a cat after cortical extirpation. The degeneration in the left homolateral pyramid is marked.

brae proved highly instructive. Sections below the lesion showed a well developed tract of large myelinated fibers, easily differentiated from the small rubrospinal sheaths in the dorsal part of the lateral funiculus, and another in the ventral funiculus. Scattered peripherally between these were fibers which gradually disappeared in the caudal half of the cord. At the first sacral level the two main tracts were still present.

Control Series.—In all control decortication preparations of the cat a prominent corticospinal tract composed of large degenerating sheaths was found (fig. 2 *H*). In two preparations stained by the Davenport method many normal axis-cylinders were observed (fig. 2 *A* and *B*). The tract was well marked below the decussation and could be followed into the lumbosacral region of the spinal cord. A few uncrossed fibers formed a homolateral corticospinal tract which reached the cervical enlargement. An anomalous condition which was noted in one specimen has been described separately.[15] A few circumolivary fibers were encountered in every cat.[16]

PHYSIOLOGIC OBSERVATIONS

Stimulation Experiments.—The excitable cortex is located lateral to the medial cerebral fissure in the anterior half and extends onto the lateral aspect of the hemisphere of the rabbit;[17] definite localization is difficult (fig. 1 *D*). Stimulation of the most anterior portion produced homolateral and contralateral movements of the face and jaw; these were the easiest of all to elicit. Stimulation posterior to this area resulted in extension, rotation or lateral flexion of the head. Stimulation farther back caused advancement and rotation of the scapula accompanied by flexion of the elbow. In two experiments cutting the muscles extending between the skull and scapula abolished advancement of the scapula and flexion of the elbow although contraction of the portion of the muscles attached to the skull could be seen. Weak movements of the wrist were observed in two instances; they could be obtained only when the rabbits had nearly recovered from the anesthesia. In one rabbit, whose responses were exceptionally sluggish, the electrodes were thrust through the cortex into the region of the lentiform nucleus, whereupon active contralateral movements of the scapula, elbow and wrist and sluggish movements of the digits were obtained. Stimulation of the lateral aspect of the cerebrum rostral to the middle of the brain resulted in movements of the jaw similar to those obtained from the cortex along the median fissure.

Responses in all experiments were weak as compared with those of cats. When movements of the face and jaw were obtained with an inductorium reading of 8 cm., those of the neck, shoulder and elbow appeared at 7 cm. Increasing the current intensified the movements; additional movements, such as coordinated running and hopping, appeared only after long continued faradic stimulation or after marked increase in strength of current. It was evident that the cortex became fatigued or refractile to stimulation rapidly; short periods of stimulation alternating with long periods of rest were necessary for best results. In no

15. Swank, R. L.: Aberrant Pyramidal Fascicles in the Cat, J. Comp. Neurol. **60**:355, 1934.

16. Swank, R. L.: The Relationship Between the Circumolivary Pyramidal Fascicles and the Pontobulbar Body in Man, J. Comp. Neurol. **60**:309, 1934; footnote 15.

17. Bremer, F.: Physiologie nerveuse de la mastication chez le chat et le lapin. Reflexes de mastication. Responses masticatoires corticales et centre cortical du goût, Arch. internat. de physiol. **21**:308, 1923.

instance was the duration of the experiment over thirty minutes. If sufficient dial was used to produce deep narcosis no response or only a few responses could be elicited by stimulating the cortex.

Stimulation of the basal ganglia ten days after decortication resulted in movements similar to those which had followed strong cortical stimulation.

Postoperative Observations.—In no case of simple cortical extirpation was paresis or increased muscle tone noted after the operation. Except for the lethargic stage occasioned by the anesthetic, it was impossible to distinguish an experimental from a normal rabbit twelve hours after the operation. At twenty-four hours most of the animals were active and seemed to have recovered completely.

In the group in which the lentiform nucleus was damaged even slightly, paresis and slightly increased tone were found. Two animals in which small lesions were confined to the anterior and superior part of this nucleus showed weakness only of the muscles of the ear, neck and forelimb on the opposite side; in Marchi preparations degeneration could not be demonstrated in the medulla oblongata and spinal cord. Lesions involving a larger part of the nucleus, especially its posterior part, resulted in more marked symptoms: the head dropped, the ear hung down, there was inability to control the foreleg in supporting the body and wrist drop was seen. In rabbits exhibiting those signs extensive degeneration of the pyramidal tract was demonstrated by the Marchi technic.

In the rabbits with small lesions in the anterior part of the nucleus all weakness and hypertonus vanished in five days. In those with larger lesions several more days was required for complete recovery. Only in the animals with nearly complete destruction of the nucleus and marked degeneration of the pyramidal tract were symptoms present longer than twelve days.

All cats exhibited transient paresis after the operations. The amount of rigidity felt when pressure was applied to the pads of the feet varied from none to well developed involvement. Much improvement was seen during the first few days after the operation, and at the end of two weeks only a few residual symptoms were observed. No indication of decortication could be found at the end of six months.

COMMENT

The present observations indicate that the rabbit has a poorly developed corticospinal tract containing a few myelinated and many unmyelinated fibers, apparently ending in the first cervical segment. In correlation with this, electrical stimulation of the cortex results in movements of muscles the nerve supply of which comes from the uppermost segments of the cord. A few rabbits showed sluggish responses of the digits, wrist and forelimb under light anesthesia. This may indicate that a few of the unmyelinated fibers pass into the cervical enlargement. On the other hand, the stimulating current may have spread to structures beneath the cortex to produce such movements. It was proved that the movements of the shoulder and elbow can be passive, although active responses of the forelimb do occur when some tracts or nuclei beneath the cortex are stimulated. The corticospinal tracts from the motor cortex proper certainly have little, if anything, to do directly with parts of the cord below the neck.

What is the source of the fibers in the pyramids which remain after simple decortication but disappear after destruction of the cortex and lentiform nucleus? They may arise in the narrow strip of cortex along the rhinal fissure (premotor area?) or in the lentiform nucleus. That some may take origin in the juxtarhinal portion of the cortex is possible. Bremer [17] and I observed movements of the jaw in the rabbit when the anterolateral part of the cortex was stimulated. Magoun, Ranson and Fisher [18] found a similar center in the cat. Wallenberg [19] traced degeneration from destruction of the cortex adjacent to the rhinal fissure of the guinea-pig through the lentiform nucleus to the lower end of the internal capsule; it ended in the midbrain. In my series of rabbits many lesions overlapped the lateral part of the cerebrum, and in two of the animals they completely severed the internal capsule without involving the lentiform nucleus appreciably (fig. 3); yet no degenerating fibers could be found below the first cervical segment.

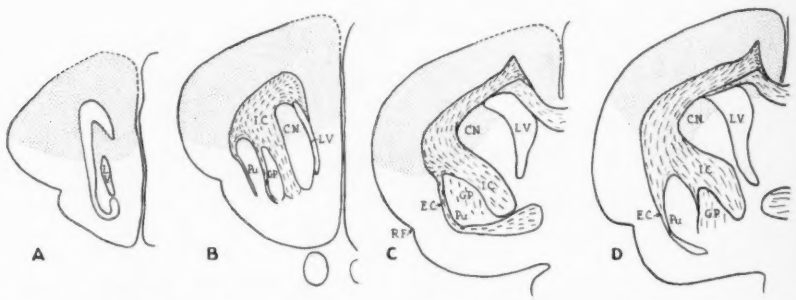

Fig. 3.—*A, B, C* and *D,* sections through the brain of a rabbit. The surface extent of the precentral motor area is represented by a broken line, and the region destroyed in one rabbit, by dots. *C.N.* indicates caudate nucleus; *E.C.*, external capsule; *G.P.*, globus pallidus; *I.C.*, internal capsule; *L.V.*, left ventricle; *Pu.*, putamen, *R.F.*, rhinal fissure.

In other experiments it was evident on stimulating the lateral cortex that no movements except those of the face and jaws could be obtained unless the electrodes were thrust into the deep parts of the brain. Therefore, it is doubtful whether all the fibers in question come from this region. The possibility that some arise in the narrow juxtarhinal cortex and pass through or beneath the lentiform nucleus has not been ruled out, but some probably take origin in the lentiform nucleus itself

18. Magoun, A. W.; Ranson, S. W., and Fisher, C.: Corticofugal Pathways for Mastication, Lapping and Other Motor Functions in the Cat, Arch. Neurol & Psychiat. **30**:292 (Aug.) 1933.

19. Wallenberg, A.: Bemerkenswerte Endstätten der Grosshirnfaserung bei Säugern, Jahrb. f. Psychiat. u. Neurol. **51**:295, 1934.

and constitute a lenticulospinal tract. To my knowledge such a tract has not been described in higher mammals. Wilson's [20] studies on monkeys with lesions in the lentiform nucleus reveal no lenticulospinal tract, but the globus pallidus apparently was not damaged extensively. Morgan [21] placed lesions in the globus pallidus of the cat and followed degeneration no farther than the reticular nuclei of the pons and medulla oblongata. Bechterew [22] destroyed the motor cortex in the dog; after degeneration he stimulated the lentiform nucleus and obtained contralateral movements of the head, neck, foreleg and hindleg. It is possible that a pathway composed of unmyelinated or chain neurons from the lentiform nucleus to the spinal cord exists in higher forms.

There is no proof that all the degenerating fibers in the pyramidal system, which appear after cauterization of the motor cortex and after uncontrolled removal of the cortex, are corticospinal neurons. A deeper source of some has been overlooked by investigators. The fact that Laughton [11] and Magnus [23] reported paresis and hypertonus after cortical lesions in the rabbit, whereas in my series such symptoms were not observed after simple removal of the cortex but were present after lesions extending into the lentiform nucelus, shows that cortical and subcortical functions were not differentiated by these investigators.

In animals other than the rabbit most of the pyramidal tract fibers are known to dissipate in the upper part of the cervical region. The corticospinal tracts of the sheep [24] and opossum [25] resemble those of the rabbit; they end at the first cervical segment. Gray and Turner [26] and Rogers [27] found cortical representation for the tongue, jaws, head, neck and forelimbs but not for the hindlimbs in the opossum. Rogers found that stimulation of the corpus striatum two weeks after removal of excitable cortex resulted in movements of the head, neck and fore-

20. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427, 1914.

21. Morgan, L. O.: The Corpus Striatum: A Study of Secondary Degeneration Following Lesions in Man and of Symptoms and Acute Degenerations Following Experimental Lesions in Cats, Arch. Neurol. & Psychiat. **18**:495 (Oct.) 1927.

22. Bechterew, W.: Die Funktionen der Nervencentra, Jena, Gustav Fischer, 1909.

23. Magnus, R.: Körperstellung, Berlin, Julius Springer, 1924.

24. King, J. L.: The Pyramid Tract and Other Descending Paths in the Spinal Cord of the Sheep, Quart. J. Exper. Physiol. **4**:133, 1911.

25. Turner, E. L.: The Pyramidal Tract of the Virginian Opossum, J. Comp. Neurol. **36**:387, 1924.

26. Gray, P. A., Jr., and Turner, E. L.: The Motor Cortex of the Opossum, J. Comp. Neurol. **36**:375, 1924.

27. Rogers, F. T.: An Experimental Study of the Cerebral Physiology of the Virginian Opossum, J. Comp. Neurol. **37**:265, 1924.

limbs. Several investigators [28] have shown that the number of pyramidal tract fibers per gram of muscle supplied the first four spinal segments of man, dog and rat is about four times that supplied the six segments immediately below. Weil [28b] suggested that the upper part of the cervical region constitutes an important center for regulation of postural and righting reflexes in relation to the limbs and trunk. They believed that cortical control of these spinal reflex centers is more urgent than for other parts of the spinal cord.

Lassek [29] and DeLozier [30] have shown that the volume and sectional area of gray in proportion to white matter in the first three cervical segments is great in the rabbit. Numerous large neurons of Malone's [31] motor type occupy the large reticular formation. It is possible that the pyramidal fibers ending in this region make synaptic connection with these cells. Perhaps these are the neurons which give rise to the well developed cervical reticulospinal tract of the lateral funiculus. This tract, observed in the spinal cord of the sheep [24] and rabbit, is not of cortical origin; it probably does not arise in the red nucelus, because myelin sheaths of rubrospinal fibers are much smaller. The possibility that it comes from the reticular formation should be considered.

CONCLUSIONS

The corticospinal tracts of the rabbit arising in the anterior half of the cerebrum lateral to the median fissure end in the first cervical segment of the spinal cord; a few fibers may reach the third. They contain a few small myelinated and many unmyelinated fibers.

Light faradic stimulation of the motor cortex of the rabbit results in contralateral movements of the face, jaw, neck and forelimb only. The movement of the forelimb is caused by contraction of muscles attaching the limb to the trunk and base of the skull.

The pyramidal system of the rabbit contains fibers other than those from the motor cortex. They are larger and more numerous than those of the corticospinal tracts. Some may arise in the anterolateral part

28. (*a*) Weil, A., and Lassek, A.: The Quantitative Distribution of the Pyramidal Tract in Man, Arch. Neurol. & Psychiat. **22**:495 (Sept.) 1929. (*b*) Lassek, A. M.; Dowd, L. W., and Weil, A.: The Quantitative Distribution of the Pyramidal Tract in the Dog, J. Comp. Neurol. **51**:153, 1930. (c) King, J. L.: The Corticospinal Tract of the Rat, Anat. Rec. **4**:245, 1910.

29. Lassek, A. M.: A Comparative Volumetric Study of the Gray and White Substance of the Spinal Cord, J. Comp. Neurol. **62**:321 (Oct.) 1935.

30. DeLozier, L. C.: A Comparative Study of the Lateral Reticular Nucleus in the Upper Three Cervical Spinal Cord Segments, Anat. Rec. **55**:53, 1933.

31. Malone, E. F.: Recognition of Members of the Somatic Motor Chain of Nerve Cells by Means of a Fundamental Type of Cell Structure, and the Distribution of Such Cells in Certain Regions of the Mammalian Brain, Anat. Rec. **7**:67, 1913.

of the hemisphere along the rhinal fissure, but most appear to take origin in the caudal two thirds of the lentiform nucleus and constitute a lenticulospinal tract. They end in the cervical enlargement of the spinal cord.

In the experiments here reported faradic stimulation of the lentiform nucleus resulted in contralateral movements of the shoulder, elbow, wrist and digits.

Simple cortical destruction or that accompanied by damage of the caudate nucleus resulted in neither paresis nor hypertonus. Small lesions in the lentiform nucleus anterior to the globus pallidus caused mild symptoms, often persisting less than five days and unaccompanied by an increase in degeneration of the pyramidal tract. On the other hand, destruction of the caudal two thirds of the lentiform nucleus involving the globus pallidus resulted in marked paresis and hypertonus, which persisted eight days or more, depending on the extent of damage. Marked degeneration of the pyramidal tract was found.

I believe that cortical control of the trunk and hindlimbs is effected through synaptic connections with neurons in the reticular formation of the medulla oblongata and cervical portion of the spinal cord by means of a cervical reticulospinal tract.

GLIOBLASTOMA

A POINT OF VIEW CONCERNING TREATMENT

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This presentation refers particularly to the treatment of glioblastoma which can be verified at operation or, if necessary, definitely identified by an immediate microscopic examination. The conclusion which I have reached in regard to surgical treatment is at variance with the view held by some neurosurgeons in America and probably also by some in England. A few years ago I formed the opinion that operation was futile and better left undone if one could be reasonably certain of the diagnosis preoperatively. I think otherwise at the present time. The former impression developed because of a number of surgical experiences exemplified by the following case:

CASE 1.—A well educated man aged 45 had a short history of intracranial pressure. Operation showed that the frontal convolutions were flattened and pale, and a deep glioblastoma was verified by incising the cortex and removing a small amount of tumor. A sufficient mass of tissue was not removed to relieve the tension in the brain. A large subtemporal decompression was left. Previous to five or six years ago this was the type of operation which I was accustomed to perform when dealing with a glioblastoma. Symptoms were relieved for six or eight weeks; the decompression then became tense, and after a short time the patient was confined to bed. He lived for six months with an increasingly disfiguring deformity as the bone flap and decompression bulged. During the last four months he was unable to communicate with his wife because of clouded intellect. The end was a relief to all concerned. If this was all that could be accomplished by operation, how much better if the patient had died shortly after the symptoms returned, that is, when the decompression became tense. The decompression, although it probably prevented death immediately after operation, prolonged an existence which no one would care to contemplate.

What, then, can be done for a patient with glioblastoma? It must be admitted that a permanent cure cannot be obtained. After operation relief from symptoms for a period of months is the most that can be expected, and if this is to be worth while it must not be followed by a prolonged period when the patient, deformed by a bulging decompression and flap, has total disability and is a financial burden on relatives or on the community.

Read before the Association of British Neurological Surgeons in London, Aug. 3, 1935.

In certain cases operation should not be considered, apart from an exploratory bur hole to rule out definitely a meningioma or subdural hematoma. A simple external decompression should not be performed. This will do little but prolong a useless existence. Headache can be controlled by large doses of sedatives, and in any event the severe headache caused by an increasing intracranial pressure persists for some weeks or a few months only and then tends to disappear. Often the patient has passed through this period of severe headache before a surgeon is consulted.

In most cases I believe it is worth while to advise operation on the understanding that an operative procedure will be attempted which will probably enable the patient to carry on in a satisfactory manner with little or no disability and without deformity for several months. After this period of relief there should not be a period of prolonged useless existence. In my opinion this limited but satisfactory result can be obtained in many cases by the following procedure: Sufficient tissue is removed to relieve the impaired circulation of the brain. Usually this involves the removal of a mass of tumor and overlying brain, approximately the size of a small orange. When this is done all tension is relieved, and the brain tends to drop away from the dura. After this is accomplished no attempt is made to eradicate deeper parts of the tumor. The purpose of the operation is accomplished, and there is no need of running the risk of deep hemorrhage, which may cause death as a result of operation. The dura is then carefully sutured. When the space left after this resection fills with tumor, symptoms return, but life is not then unduly prolonged because the dura has been closed tightly. In principle this may be termed an internal decompression in contrast to the other procedure, in which intracranial pressure is largely controlled by an external decompression, a procedure which I thoroughly condemn as a treatment for glioblastoma because of the resulting deformity and the prolongation of life long after the time when death would be a relief.

The danger of immediate death from operation is not increased when a satisfactory internal decompression is performed. The following case illustrates the result which one may reasonably expect to obtain.

CASE 2.—A man aged 45, well educated, married, with three small children, was operated on during the first week of November 1934. Figure 1 shows the situation and estimated extent of the glioblastoma. A large mass of tumor and overlying brain was resected, leaving a cavity the size of a small orange; the dura was closed tightly and the bone flap tied in place. Before operation the patient was bedridden and completely aphasic, and his right arm was spastic. In three weeks he was up and about, cheerful and taking a marked interest in his affairs, although still suffering from marked motor aphasia and weakness of the

right arm. He improved rapidly. I was in close contact with this patient and his wife until his death, seven months after operation; six of the seven months were well worth while. The patient arranged his business affairs; he was able to preside at several meetings and to make a short speech. His friends felt that he was well and enjoyed his company. There was no disfiguring decompression or loss of hair due to roentgen treatment. The end came quickly; there was a period of headache and vomiting for a day or two and then clouding of intellect and loss of consciousness, death occurring in a week. The end was consequently in striking contrast to that of the first patient, in whom a large external decompression was left.

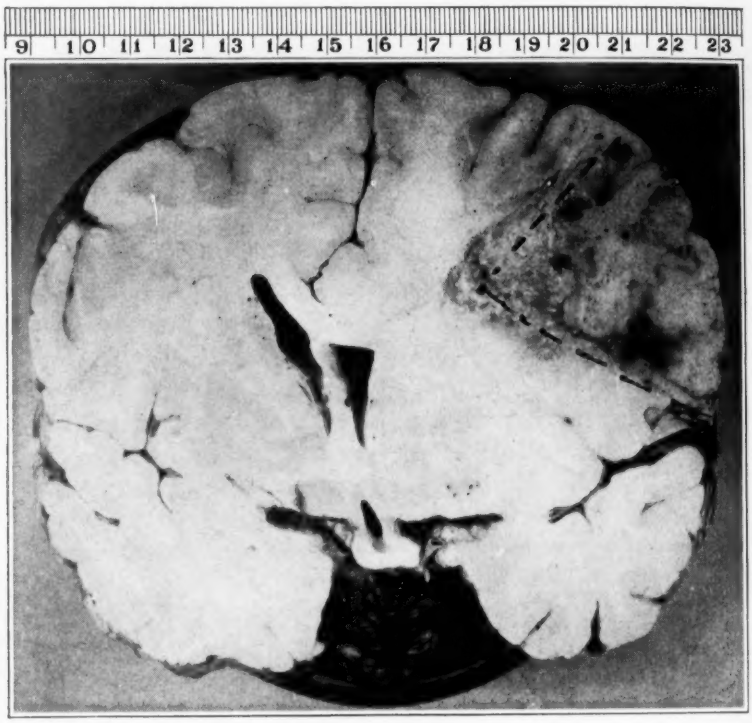

Fig. 1.—(case 2).—The brain obtained seven months after resection of the tumor as illustrated by lines of dashes. In seven months the space left by this resection had refilled. The appearance at autopsy was practically identical with that seen at operation.

The principle of operation outlined here is, in my opinion, the most satisfactory method available of treating a patient with a glioblastoma in the cerebral hemisphere. Furthermore, in many instances the disfiguring loss of hair resulting from roentgen therapy more than counterbalances any relief which may be obtained from that form of treatment.

Certainly, in this particular patient the loss of hair would have been most disconcerting.

It is understood, of course, that other tumors may require an operation different in principle. A working knowledge of the pathology of tumors is essential, and for this a large debt is owing to Cushing and Bailey. For instance, an external decompression alone may be the operation of choice when dealing with an astrocytoma, as exemplified by the following case.

CASE 3.—The patient had jacksonian seizures involving the right arm for four years before operation. There was then some moderate choking of the disks and shifting of the ventricular system to the right. At operation (fig. 2) the tumor was considered to be not a glioblastoma but an astrocytoma. This was verified by microscopic examination. The tumor was not cystic. Radical resection would have increased the patient's disability. A decompression only was made; the choking of the disks disappeared, and, apart from fairly frequent jacksonian seizures, the patient was well four and one-half years after operation and eight and one-half years after the onset of symptoms.

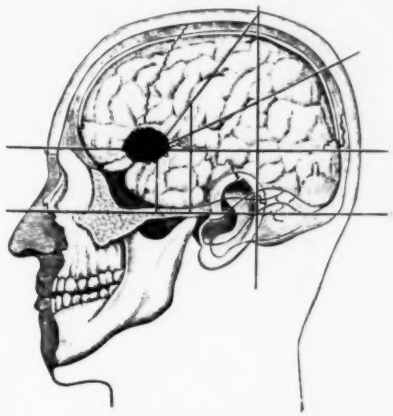

Fig. 2 (case 3).—Situation of the astrocytoma.

Again, I reiterate, a patient with a glioblastoma should not undergo an external decompression if it can be avoided. Any relief obtained is more than counterbalanced by the deformity and prolongation of life after a period when it would be better for all concerned if the patient were dead.

Some surgeons may be of the opinion that no patient with a glioblastoma should be operated on. I know, however, from the experience gained by talking to these patients and their relatives that they feel that a result comparable to that reported in case 2 is worth while.

SUMMARY AND CONCLUSION

A glioblastoma should be resected in a sufficiently radical manner to leave a large cavity. This procedure may be termed an internal decompression. Such a procedure usually gives a sufficiently long period of real relief to make the operation worth while. The dura should be closed throughout when possible so that an external decompression is not left, as this may prolong life for months after the time when life becomes a burden. On the contrary, a simple external decompression without resection may be the operation of choice when dealing with a more benign tumor, such as a solid astrocytoma.

PRIMARY DEGENERATION OF THE CORPUS CALLOSUM

(MARCHIAFAVA'S DISEASE)

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AND

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Extensive primary degeneration of the corpus callosum has been described in about forty male Italians. Since Marchiafava and Bignami [1] reported the first three cases on record, in 1903, the condition has usually been called Marchiafava's disease. It is characterized by demylinization of nerve fibers, with relative retention of axis-cylinders; the lesions occur invariably in the corpus callosum, but sometimes in other parts of the brain as well. These lesions are symmetrically located on the two sides of the brain. In cases in which a clinical history has been obtained the symptoms were found to be both psychic and somatic. The patients were usually in or past middle age and frequently had been excessive users of alcohol. In the present report we shall record an additional case.

HISTORY

In 1903 Marchiafava and Bignami [1] reported briefly the observations at autopsy in three cases, one of which had first been described by Carducci in a doctor's thesis in 1898, and gave brief clinical histories of two of the patients. These patients showed degeneration of the corpus callosum only. Bignami [2] in 1907 added the report of another case, with the new observation of similar degeneration in the anterior commissure. In 1910 Rossi [3] described two other cases rather fully, placing more emphasis on the detailed microscopic features. The follow-

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1. Marchiafava, E., and Bignami, A.: Sopra un' alterazione del corpo calloso osservata in soggetti alcoolisti, Riv. di pat. nerv. **8**:544, 1903.

2. Bignami, A.: Sulle alterazione del corpo calloso e della commissura anteriore ritrovate in un alcoolista, Policlinico (sez. prat.) **14**:460, 1907.

3. Rossi, O.: Sull 'istologia patologica di una speciale alterazione descritta da Marchiafava nel corpo calloso degli alcoolisti, Riv. di pat. nerv. **15**:346, 1910.

ing year Marchiafava, Bignami and Nazari [4] described the condition more extensively, basing their opinions on twelve examples, including the four that they had previously described. In the next few years four other reports [5] were published by different authors, although the condition described by one of these, Sarteschi, was probably not the same disease. We have not been able to obtain the original communications. In 1915 Bignami and Nazari [6] again discussed the topic and reported nineteen new cases, including two that had been previously published by Milani.[7] At this time they described subcortical degeneration in several of their cases. Mingazzini [8] in 1922 discussed this type of degeneration at length in his monograph on the corpus callosum and briefly reported four more examples, two of which had been observed by Gianelli and one each by Bonfiglio and Milani. The most recent presentation that we have found in the literature is that of Guccione [9] in 1929. Marchiafava [10] in 1933 briefly surveyed this type of degeneration without giving a comprehensive discussion. He reported no new cases but mentioned that two new cases had been observed by Nazari in 1932. The latter have apparently never been published. It thus appears that forty-three cases of this disease have been observed. However, since Milani's and Gianelli's cases may have been duplicated, the number may be forty-one or forty-two.

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4. Marchiafava, E.; Bignami, A., and Nazari, A.: Ueber System-Degeneration der Kommissurbahnen des Gehirns bei chronischen Alkoholismus, Monatschr. f. Psychiat. u. Neurol. **29**:181 and 315, 1911.

5. Cesaris-Demel: Atti d. Soc. ital. di pat. in Pisa, 1913. Giannelli, in Mingazzini, G.: Lezioni di anatomia clinica dei centri nervosi, Turin, 1912. Marchiafava, E.: Conferenza sulla patologia dell' alcoolismo, Milano, 1913. Sarteschi: Sopra una speciale alterazione della sostanza bianca in un caso di alcoolismo cronico, Riv. sper. di freniat. **37**:115, 1911. The first three of these references have been taken from Bignami, A., and Nazari, A.: Sulla degenerazione delle commissure encefaliche e degli emisferi nell' alcoolismo cronico, Riv. sper. di freniat. **41**:81, 1915. A further reference, given by Guccione (Su un caso di degenerazione primaria del corpo calloso, Riv. di pat. nerv. **34**:722, 1929) we have not been able to find, even though the journal was available.

6. Bignami, A., and Nazari, A.: Sulla degenerazione delle commissure encefaliche e degli emisferi nell' alcoolismo cronico, Riv. sper. di freniat. **41**:81, 1915.

7. Milani, A.: Patologia del corpo calloso, Tesi di Lib. Doc. nella R. Univ. di Roma, 1914. (The original was not available.)

8. Mingazzini, G.: Der Balken, Berlin, Julius Springer, 1922.

9. Guccione, F.: Su un caso di degenerazione primaria del corpo calloso, Riv. di pat. nerv. **34**:722, 1929.

10. Marchiafava, E.: The Degeneration of the Brain in Chronic Alcoholism, Proc. Roy. Soc. Med. **26**:1151, 1933.

INCIDENCE

As was previously stated, all the patients have been male Italians. The age range was from 39 to 82.[11] The average age at death in the cases in which the age was stated, including ours, was 59.9 years. There is no real modal point, since twelve patients died in the fifth decade, nine in the sixth and ten in the seventh. Whenever the clinical history has been obtained it has been noted that the patient was a heavy drinker, either of wine or of wine and distilled liquor. In some cases excessive use of alcohol by the parents was recorded. In a few instances, although the amount of alcoholic beverages consumed was not extraordinary, it was known that the patient was unusually susceptible to their influence. The predominance of a history of alcoholism and the absence of other recognizable causative factors, such as syphilis, trauma, the excessive use of tobacco and other known toxins, have led most writers to agree in considering this disease an alcoholic condition.

SYMPTOMATOLOGY

The symptom picture shows much variation from case to case, although there are outstanding points of resemblance. Since the clinical history is sometimes lacking and when given is variable in extent, it is impossible to make any statistical study of the symptoms. Psychic disorders are frequent and are noted almost always in a case in which a complete history is obtained. Frequently they are the first indication of disease, and often they are severe enough to require treatment in a hospital for persons with mental disorders. Some patients subsequently show sufficient improvement to be discharged from such institutions, but others become worse. Emotional disorders, including states of exaggerated excitability and irascibility, leading to acts of violence, are prominent. Other patients may show marked apathy. Moral perversions and sexual misdemeanors are often observed. Intellectual decay is usually progressive and may lead to confusion and dementia. Anxiety, delusions and hallucinations have been reported in a few cases.

The most constant somatic finding is convulsions of an apoplectiform or epileptiform type. In some patients these occur frequently, while in others there may be but one severe attack, initiating a period of rapid deterioration. Bignami and Nazari [6] reported one or more convulsions in twenty-one of the twenty-two patients from whom they could obtain information on this point, although other authors have not described this symptom so constantly. Tremors, dysarthria, transitory hemiparesis, brief attacks of weakness without loss of consciousness,

11. The age of Guccione's patient was once stated as 32 and once as 82. Evidently the first figure is a typographical error, as internal evidence suggests that 82 is correct.

paresis of the legs and variable reflex changes have been observed in different patients. Sensory disturbances, except headaches, have not been reported. Autonomic disorder may be present in the form of impotence or incontinence. Bignami and Nazari emphasized the severe disorders of nutrition in the terminal stages.

COURSE

The course is variable, usually from three to six years, but it is difficult to make precise statements on this point. The development is insidious, and the early psychic symptoms are easily confused with those of alcoholic intoxication, which is a frequent occurrence in many of these patients. The condition shows some tendency to remissions and exacerbations, in both the somatic and the psychic sphere. Some patients who are forced to give up work are later able to resume it. The disease usually terminates in a period of extreme weakness and gradual loss of consciousness leading to coma, often preceded by one or a series of convulsions. The cause of death is usually stated to be bronchopneumonia, although other conditions, such as uremia and carcinoma, also occur. It is notable that syphilis is infrequently present.

PATHOLOGIC OBSERVATIONS

The condition is not recognizable until autopsy. Apart from the changes in the brain, the observations are variable, including the usual type of minor abnormalities noted in patients of this age group. Patches of bronchopneumonia are frequent. There may be slight or moderate sclerosis of the blood vessels.

Grossly, the uncut brain usually appears fairly normal. The pia is sometimes slightly thickened and occasionally hyperemic. The cerebral arteries often, but not always, show some sclerosis. Slight cortical atrophy is sometimes noted. However, nothing on the surface of the brain gives any hint of the changes seen on section.

When the brain is cut, macroscopic changes are easily observed, always in the corpus callosum, although in varying extent, and sometimes in the anterior commissure, brachium pontis and subcortical regions. The anterior portion of the corpus callosum appears to be rather sharply divided into three laminae, of which the dorsal and ventral are normal in color and consistency, while the middle is softer and pinkish or grayish. This condition of the middle layer is sometimes present throughout the corpus callosum. In many cases, in the posterior parts of the corpus callosum the abnormal area disappears in the region of the midline, leaving symmetrical lesions on the two sides, extending backward for varying distances. In only one case was the anterior portion less extensively affected than the posterior. The abnormal area

usually stops abruptly at or near the lateral margins of the corpus callosum. The soft, pinkish lamina ordinarily occupies about two thirds of the dorsoventral extent of the corpus callosum. When there are lesions in other parts of the brain, they have a similar appearance and are always symmetrical. The detailed histologic features of these lesions, the most conspicuous of which are demyelinization, relative retention of axis-cylinders, absence of gliosis and an apparent increase in the number of vessels, will be described later.

Dr. S. B. Wolbach gave us permission to study the brain and utilize the report of the autopsy in the case which we report, and Dr. E. C. Cutler gave us permission to use the clinical record.

REPORT OF CASE

Clinical History.—The patient, a married Italian man, aged 54, a laborer, was brought to the Peter Bent Brigham Hospital (the surgical service) on Oct. 26, 1933, in a semicomatose condition of three days' duration. He had enjoyed good health until three years before entry. At that time he lost his job because of the economic depression and tended to "brood' over his inactivity, remaining otherwise "normal." After a lapse of two years the informant (son) noticed that the patient was becoming irritable and cross and would not respond to questions in his usual pleasant manner. He grew less talkative but never complained of pain or other physical phenomena. Speech remained normal, with no scanning or hesitancy. However, his irritability and reticence increased steadily. His appetite diminished, and he lost 15 pounds (6.8 Kg.) in weight in the year before entry.

From three to four months before entry motor signs were noted for the first time. Disorder of gait was first observed, with unsteadiness on the feet and occasional missteps. Shortly afterward tremors of both hands developed (the record states nothing of the effects of intention on the tremor).

Four days before admission the patient secured another job. On returning from work he became "dizzy," falling to the ground (no mention was made of possible loss of consciousness). That night "stiffness" of the arms was noted, which persisted. The next night the patient went to bed. He "couldn't move his hands" and "wouldn't talk," became "unconscious" and ate nothing. He remained in this condition until he was brought to the hospital two days later on the advice of a local physician. The family, marital and past histories were noncontributory. The patient was temperate in his habits. It is stated that he drank wine and beer in small amounts all his life.

Examination.—The significant points revealed by the physical examination were: The patient was noncooperative and comatose. At no time could any speech be elicited except "O. K." The legs, arms, abdomen and neck were noted to be spastic. The pupils were elliptic and reacted sluggishly to light. There was no paralysis, tremor or twitching. The biceps, knee and patellar jerks were hyperactive. The Babinski, Oppenheim and Gordon signs were not present, nor was ankle clonus.

The patient was seen by a medical consultant, who thought that the picture seemed more like that of a psychosis than that of an organic disease. A note made at another examination recorded that the pupils were equal and regular and reacted to light and that the extremities were slightly spastic, with a slight generalized increase in the reflexes.

Laboratory Data: The urine was normal. Examination of the blood showed a red cell count of 4,200,000 and white cell counts of from 10,700 to 12,100. The sugar content of the blood was 73 mg. per hundred cubic centimeters. The urea nitrogen content of the blood was 13 mg. The Hinton and Wassermann reactions were negative. A lumbar puncture disclosed an initial pressure of 230 mm. of water. The Pandy test gave a reaction of 1+; there was 1 cell—a lymphocyte. The total protein content of the spinal fluid was 40 mg. per hundred cubic centimeters; the Wassermann reaction was negative, and the colloidal gold test gave negative results.

The roentgen rays showed a thick cranial vault without localized changes or signs of pressure and with no localizing signs of tumor. An encephalogram was taken, but only 50 cc. of air could be injected before the patient's condition became serious. The roentgen rays at this time showed the ventricles to be poorly filled but normal in size, shape and position, as far as could be determined. The subarachnoid space over both frontal lobes was definitely wider than normal, suggesting bilateral cortical atrophy.

Course.—Respiratory difficulty developed, with signs of consolidation at the base of each lung. These signs disappeared after five days, but the patient's condition grew worse. The respiratory rate rose to 44; the pulse became weaker, and the patient died. The temperature had not been elevated. A psychiatric consultant who saw him before death could come to no conclusion as to the condition.

General Observations at Autopsy (Fourteen Hours Post Mortem).—Apart from the changes in the brain, there were pulmonary consolidation, and numerous minor pathologic alterations which were not relevant to this disease. When the brain was removed the venous sinuses of the dura were clear, containing no antemortem thrombi. There was mild atrophy of the frontal and parietal cortex, with an increased amount of clear cerebrospinal fluid in the subarachnoid space over the frontal lobes. There was a small ecchymosis in the most posterior portion of the right lobe of the cerebellum, immediately above the lateral sinus, measuring 1.5 by 0.5 cm. and about 3 or 4 mm. in depth. The blood vessels of the base were in excellent condition, being soft and pliable, without occlusion or atheromatous plaques. The main branches of the middle and anterior cerebral arteries were traced at autopsy and found to be normal. At a later time reexamination of the anterior cerebral arteries was made. They seemed entirely free from disease.

The brain, which was hardened in solution of formaldehyde and cut into thick slabs in the frontal plane, was received by us from Dr. S. B. Wolbach. Only a few pieces had been removed for microscopic examination. The responsibility for all the subsequent description rests entirely with us.

Study of the Brain.—After gross examination, three slabs, entire cross-sections of the brain, were set aside for study of the whole brain. Smaller blocks were cut from the remainder and embedded in pyroxylin. Apart from areas sectioned because they showed examples of the lesions, the following locations were included: the superior, middle and inferior frontal gyri; the precentral and postcentral gyri; the insula, claustrum and lenticular nuclei; the area striata and the area peristriata; the hippocampus, amygdala and inferior temporal gyrus, and the cerebellum. Sections of the thalamus and caudate nuclei were included with blocks of the lesion. In addition, frozen sections were made of the cortex of the frontal and the occipital lobe, as well as of lesions. A few sections of the medulla oblongata were cut from the paraffin blocks used by the hospital.

The following stains were used: hematoxylin and eosin; cresyl violet and thionine, for cell structure; the Weil stain, for myelin sheaths; the Davenport

stain, for axis-cylinders; Foot's impregnation, for reticulin; Globus' modification of the Cajal impregnation, for astrocytes, and the sudan III or IV stain, for fat. Through the instrumentality of Dr. Stanley Cobb, sections of the whole brain were stained for myelin by the Weigert method.

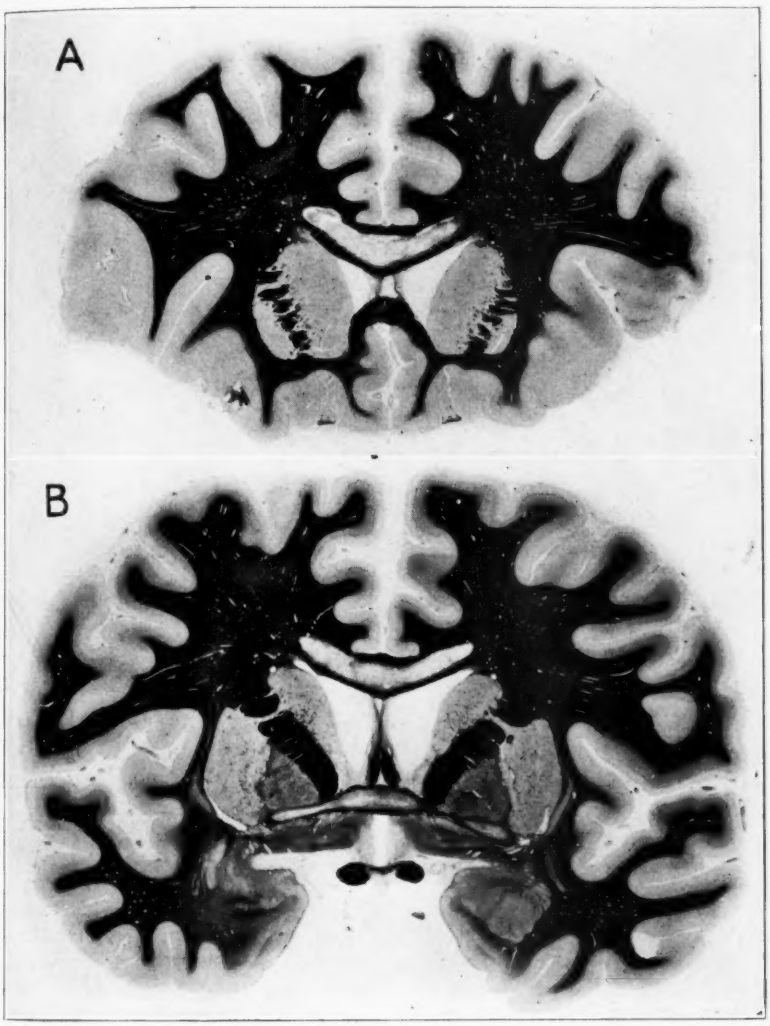

Fig. 1.—*A*, section through the head of the caudate nucleus. Weigert's stain. *B*, section through the anterior commissure. Weigert's stain. Degeneration in the optic chiasm should be noted.

Gross Pathologic Changes: The principal gross pathologic features may be well seen from the illustrations of sections of the whole brain stained by the method of Weigert. The typical distribution of lesions in the corpus callosum

stood out markedly. This structure was degenerated throughout the entire oral-caudal plane and showed a normally myelinated dorsal and ventral zone, while the middle lamina was practically entirely without myelin. The myelin sheaths were somewhat more resistant in the midline, especially in sections through the splenium. The corpus callosum as a whole was not diminished in the dorso-ventral extent. The tissue in the degenerated areas, however, was highly rarefied, though not collapsed. There were numerous small cysts and cavities.

The margins of the severe degeneration stopped rather abruptly in the centrum ovale, although, as will be seen in the description of the microscopic observations, there was a considerably more gradual transition into normal tissue than appeared here. This applies to both the lateral and the dorsoventral margins.

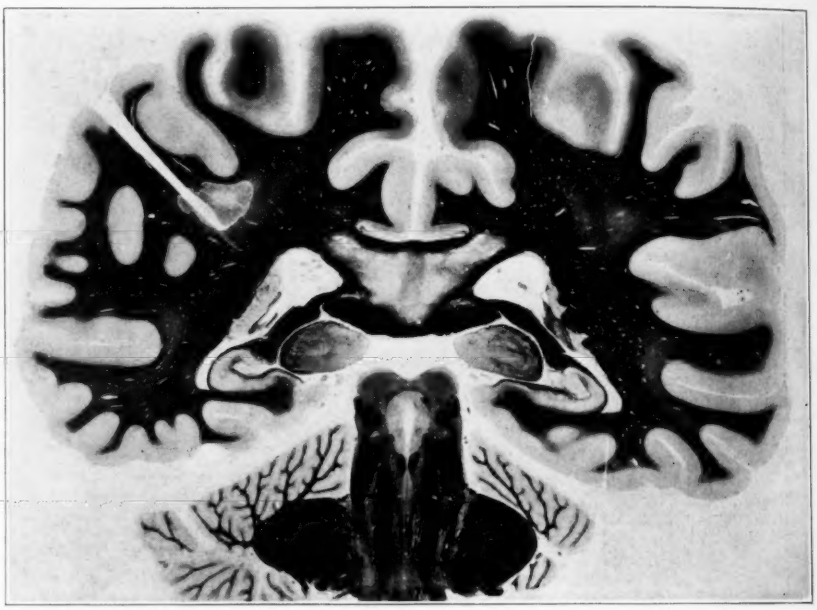

Fig. 2.—Section through the splenium of the corpus callosum. Weigert's stain.

In figure 1 *A*, which shows a section through the head of the caudate nucleus, there can be seen rather diffuse and symmetrical loss of myelin in the centrum ovale. In the unstained block fixed in solution of formaldehyde there were small, distinctly softened areas in this location which were rather well circumscribed. In stained sections, however, circumscribed areas were not visible. Instead, the loss of myelin appeared to be diffuse, and the areas which were slightly soft to the touch were not marked off in any special manner.

In figure 1 *B*, which shows a section through the anterior commissure, the latter structure is seen to exhibit a type of degeneration similar to that of the corpus callosum. There are narrow dorsal and ventral zones which retain a normal degree of myelinization, while the central lamina shows the same cystic appearance, with severe loss of myelin. This loss is not complete, however, and is somewhat less marked in the midline. In this section, too, may be observed the diffuse

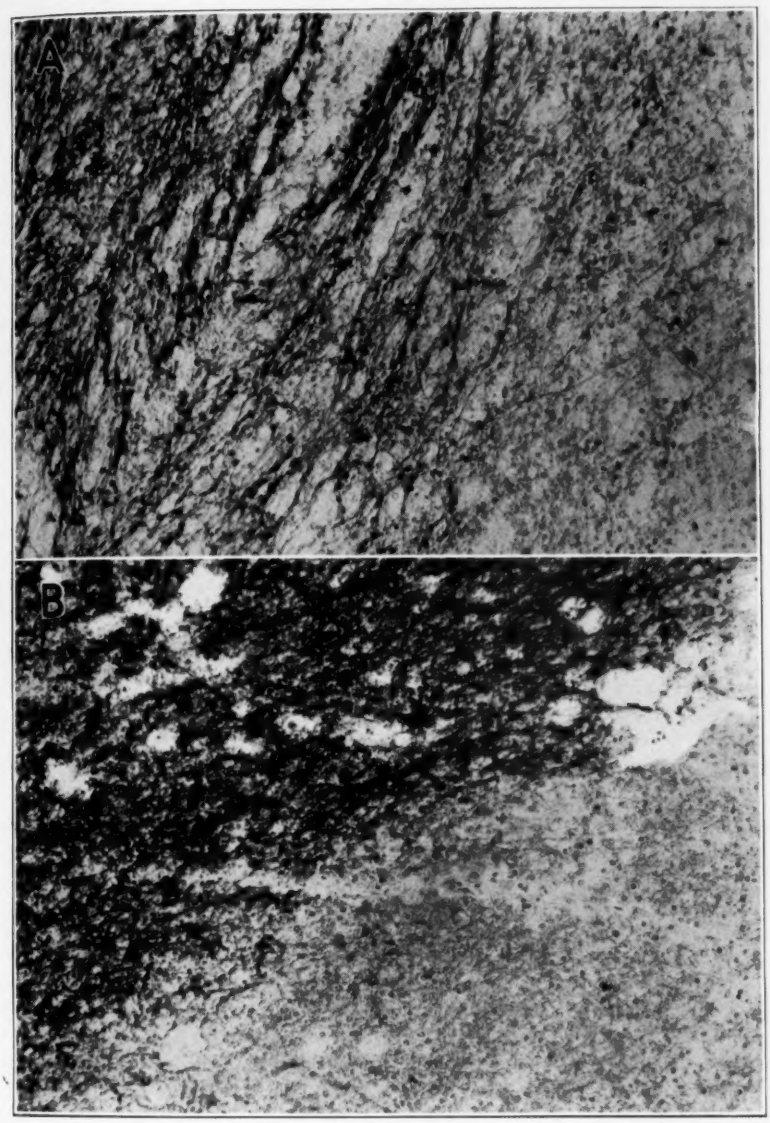

Fig. 3.—*A*, margin of a callosal lesion. Weil's stain; × 140. *B*, margin of a lesion in the centrum ovale of the type shown in the left hemisphere in figure 2. Weil's stain; × 140.

symmetrical demyelinization in the centrum ovale. Again, localized areas which are soft to the touch do not stand out distinctly. Degeneration in the optic chiasm should be noted.

In figure 2, which shows a section through the splenium of the corpus callosum, a softened area stands out sharply on the left side, pierced by a split, which is an artefact. This focus might at first glance be confused with a buried gyrus of the cortex. On the opposite side there is a smaller softened area, which forms the center of a more diffuse patch in which there is demyelinization. Diffuse loss of myelin is visible in the subarcuate region of the temporal lobes of each side. It is to be noted that the hippocampal commissure seems to be slightly invaded by the area of degeneration. The tapetum of each side is normal.

In unstained slabs of the brain the demyelinated areas in the temporal lobe, lying beneath the arcuate fibers were separable from the rest of the white matter by their distinct grayish tint. Similar areas were visible in the occipital lobe, under the calcarine cortex.

Microscopic Examination: The microscopic picture was that of a demyelinizing encephalopathy, with preservation, to a large extent, of the axis-cylinders, slight gliosis, and absence of inflammatory changes, and with a definitely restricted, highly symmetrical distribution. The activity and intensity of the degenerative process varied widely in different parts of the lesions. Those in the corpus callosum were, on the whole, much more advanced than those in the centrum ovale.

The myelin sheaths in the central part of the callosal foci were almost entirely absent. Occasionally, faintly stained fragments of myelin sheaths persisted in the depths of the lesion. These were extremely short, fragmented and very pale. The margins of the lesion were, for the most part, not sharply circumscribed but faded off gradually into the relatively normal dorsal and ventral zones. Figure 3 *A* shows such a marginal zone. A few isolated myelinated fibers can be seen penetrating the demyelinated zone, passing amid numerous glia cells the nuclei of which are stained. These fibers pass sometimes singly and sometimes in small bundles. The fibers show distinct abnormalities in the form of varicosities with globular and oval swellings which are sometimes extremely pronounced. Such abnormalities were visible to a less degree even in the so-called normal zones of the corpus callosum. The abnormalities diminished in intensity from the margin of the lesion to the periphery of the corpus callosum.

In the centrum ovale the demyelinization, in the sections examined, was never complete. In the small blocks selected for study the lesions were more circumscribed than those in the corpus callosum. Macroscopically, they were colored a very pale blue with the Weil stain, in contrast to the complete decolorization in the corpus callosum. Cross-cut myelin sheaths, rather pale and abnormal, were present in moderate numbers over the entire lesion. Figure 3 *B* shows the marginal zone in the centrum ovale, at the same magnification as that used for figure 3 *A*. The margin is relatively sharp. The diffuse gray tone of the lower right of the picture represents the pale blue of the remaining myelin sheaths. In the lower left a few swollen fibers stand out clearly at the edge of the lesion. The numerous small cysts and cavities in the normal white matter are widespread. To what degree they were artefacts is difficult to state. It is of interest, however, that their presence has been noted by previous observers in normal as well as in degenerating parts of the brain in this condition.

The axis-cylinders had suffered relatively little compared to the myelin sheaths. *A* and *B* of figure 4, which are photomicrographs of sections from areas of complete demyelinization in the corpus callosum, show the persistence of the axis-

cylinders. Pathologic alterations, especially tortuosity, beading, bulbous enlargements, fusiform swellings and fragmentation are evident. These changes were present to a less degree in those zones of the corpus callosum which appeared relatively normal when treated by myelin stains. They were totally absent in those parts of the brain untouched by the disease process, such as the thalamus, basal ganglia and cortex.

In our preparations there were no areas where axis-cylinders were totally absent. Even in areas where, by the Nissl stain, a focus seemed to be completely softened (as in figure 5 *A*), with densely packed gitter cells, appropriate stains

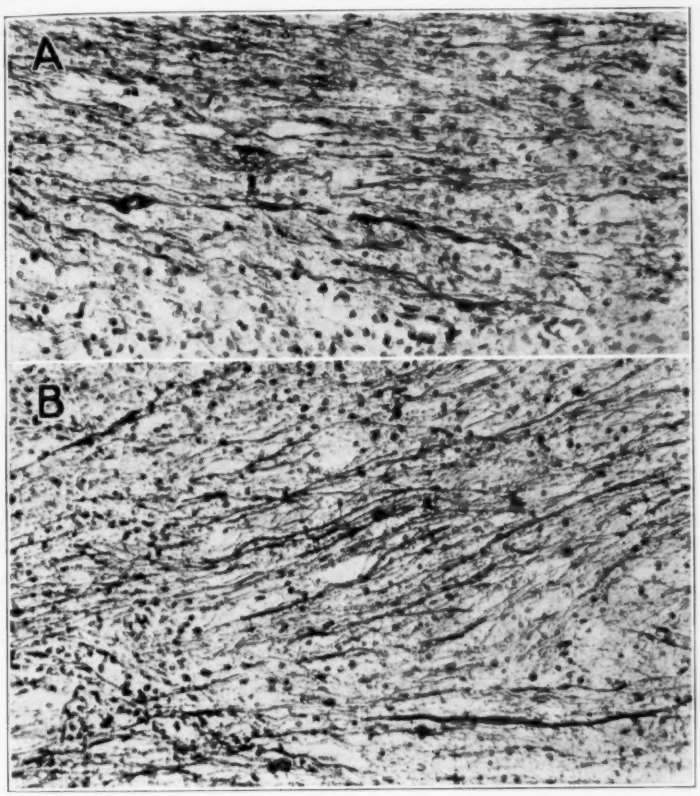

Fig. 4.—Altered axis-cylinders persisting in areas of complete demyelinization in the corpus callosum. Davenport's stain. *A*, × 190; *B*, × 140.

brought out at least a few axis-cylinders. Axis-cylinders even coursed through tissue which was highly rarefied and cystic. We have not been able to observe a single microscopic field without axis-cylinders. Over large parts of the lesions they were practically as numerous as in the relatively normal, myelinated parts of the corpus callosum, but where softening was pronounced they were reduced in number.

The cellular picture, as given by the Nissl stain, showed a wide variety of changes. Gitter cells and transitional forms of microglia cells were prominent

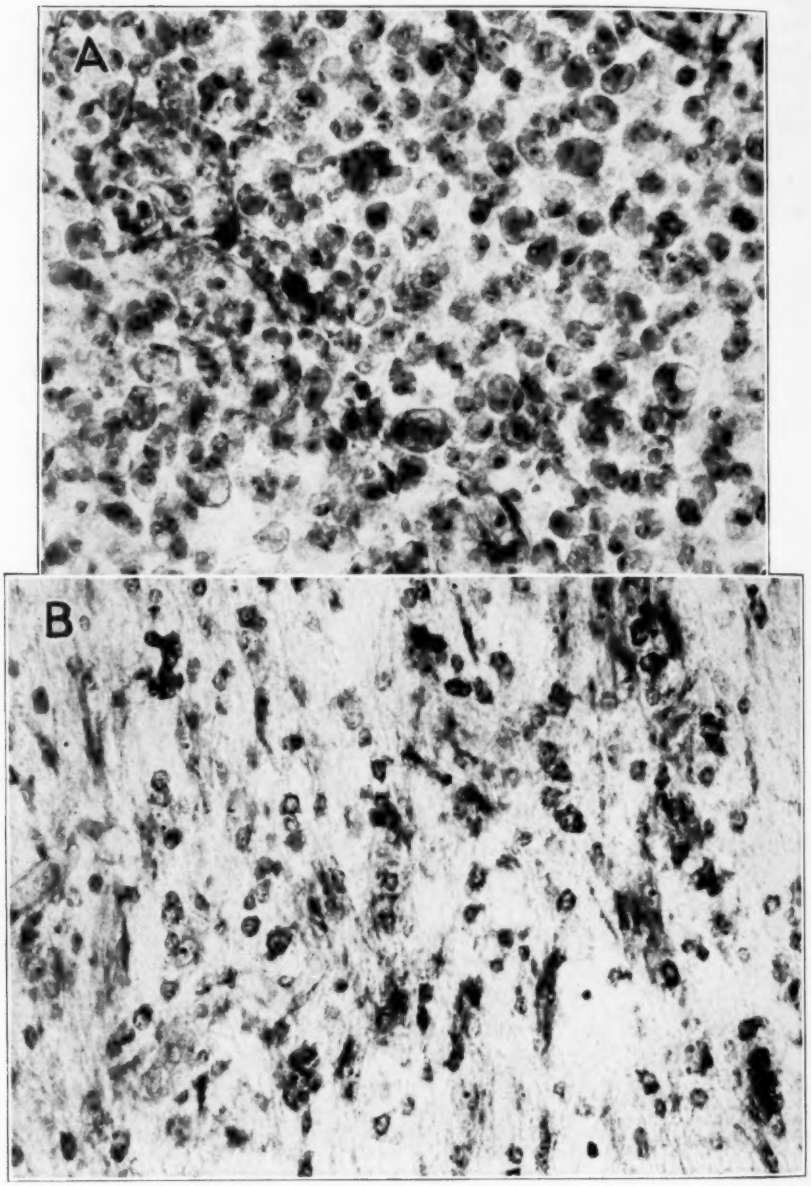

Fig. 5.—*A*, cellular picture in one portion of the corpus callosum, showing intense concentration of gitter cells. Thionine stain; × 330. *B*, field closely adjacent to that in *A*. In spite of complete demyelinization shown by the Weil stain, no gitter cells are observable. Microglia and oligodendroglia cells exhibit progressive changes. Several astrocytes are in varying stages of clasmatodendrosis, surrounded by clusters of phagocytic glia. Thionine stain; × 330.

but were not uniformly distributed. In some areas, as illustrated in figure 5 *A*, these cells were densely crowded together, mitotic figures being occasionally evident. With the exception of rare blood vessels, these granular corpuscles seemed to be the sole cellular constituents of the given field. It has already been mentioned that such an area, apparently one of complete softening, nevertheless contained recognizable axis-cylinders.

Other areas, as shown in figure 5 *B*, presented a different appearance. Figure 5 *B* is a photomicrograph of the same section as figure 5 *A* and shows an area of complete demyelinization (as judged by adjacent sections stained for myelin), not from a marginal zone. In this illustration no fully formed gitter cells are visible. Instead, the microglia cells and, undoubtedly, some oligodendroglia cells, show a great increase in number and moderate progressive changes, but they contain little or no phagocytosed lipoids.

A survey of a cross-section of the corpus callosum with low power magnification showed contiguous areas with widely different stages of microglial changes. This was shown even more strikingly by frozen sections prepared with the sudan III or IV stain. There were small patches of densely crowded large red droplets, alternating irregularly with other areas containing only a few such clusters and still others merely with scattered, fine globules or none. It was obvious that the degenerative process was proceeding at different rates, even in contiguous areas. It was further apparent that not all the tissue had reached or would reach the same end-point. An area such as that shown in figure 5 *B* was interpreted to be a rather old focus, where all the myelin had been removed. The gitter cells had been replaced by other, nonlipoid-bearing microglia cells. It may be noted in this connection that cases of this disease have been described in the literature in which microscopic examination has shown scarcely any gitter cells.

On the other hand, the field shown in figure 5 *A* is obviously a much more recent focus and one in which the destructive process was much more intense. The absence of other cellular elements and the relative paucity of axis-cylinders indicate a much more complete degeneration.

A still different picture was shown by some of the lesions in the centrum ovale. These lesions were recent but not intense. Figure 6 illustrates the degenerating tissue on the right, with numerous but not densely packed gitter cells; the advancing margin in the center, where the microglia cells are in transition to the gitter cells, and the more normal white matter on the left, where the glia show only moderately progressive changes. As has already been mentioned, degeneration had not progressed here so far as it had in the corpus callosum and was proceeding at a more even rate.

A striking feature of this disease is the practical absence of gliosis. When the whole brain is examined the lesions feel soft. With microscopic preparations the macroglia cells are, for the most part, sharply diminished in number within the confines of the degenerating areas. Such astrocytes as are present usually show regressive changes on microscopic examination. Several cells of this type are visible in figure 5 *B*. In the upper center and the lower right, glial clusters can be seen surrounding badly degenerating astrocytes. The pictures shown by the Nissl stain are confirmed by impregnation with gold chloride. In the immediately surrounding healthy tissue the astrocytes are essentially normal in number and show little reaction.

The blood vessels and mesodermal tissues showed interesting reactions. Perhaps the most extraordinary change was the apparent proliferation of vessels that

appeared here and there through the corpus callosum. This appearance, which is shown in figure 7 *A*, has been a rather constant feature in all the previous cases in which the brain has been adequately examined.

The enormous vascular richness in the lesion, which is obvious at a glance, is in marked contrast to the normal vascularity that appears in the unaffected tissue at the bottom of the picture. The section from which the photomicrograph was taken was 20 microns in thickness. The extremely convoluted and serpentine course of the vessels in a section of this thickness is unusual in any other disease. Examination of these blood vessels under higher power magnification, with different stains, showed them to be, for the most part, very thin-walled capillaries. Numerous arterioles and venules were, of course, also visible, but the majority of vessels were of capillary diameter. Such extreme vascularity was noted only in a relatively small part of the lesion, in general, near the margin of the healthy tissue.

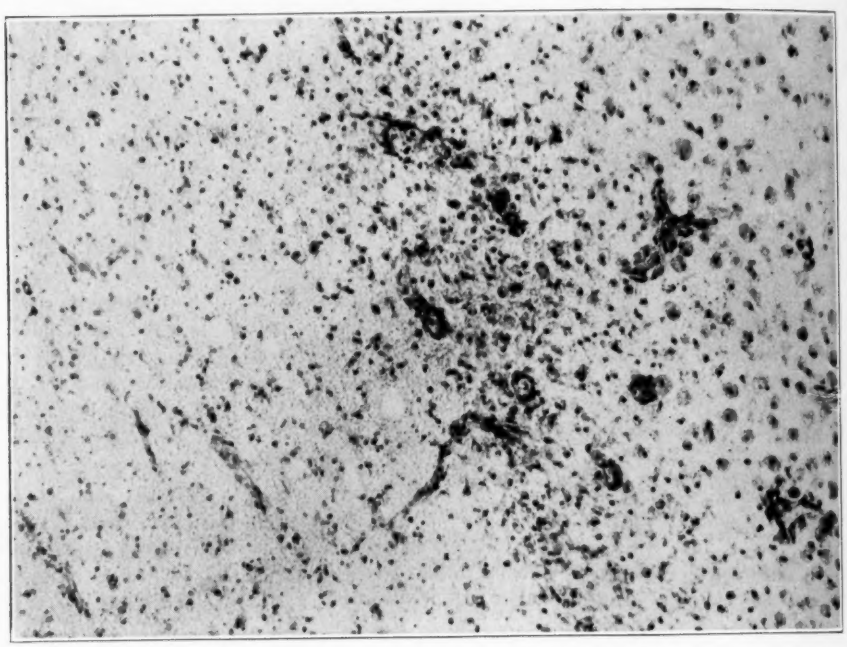

Fig. 6.—Margin of a lesion in the centrum ovale. Degenerating tissue is present on the right, with more normal tissue on the left. Gitter cells are much less numerous than in figure 5 *A*. Thionine stain; × 140.

But this vascularity will be seen only in a small portion of the whole perimeter of the lesion in a given section. It has not proved possible to adduce reasons for this fact.

In the literature a discussion has been waged as to whether this type of vascular formation represents a new growth of blood vessels or merely an apparent increase due to the atrophy of the ectodermal tissue and a consequent heaping up of the blood vessels contained therein. Undoubtedly, the latter factor does play a rôle, but true proliferation cannot be doubted.

Careful examination of figure 7 *A*, which shows a section impregnated for reticulin by the Foot method, will disclose several areas where there is free pro-

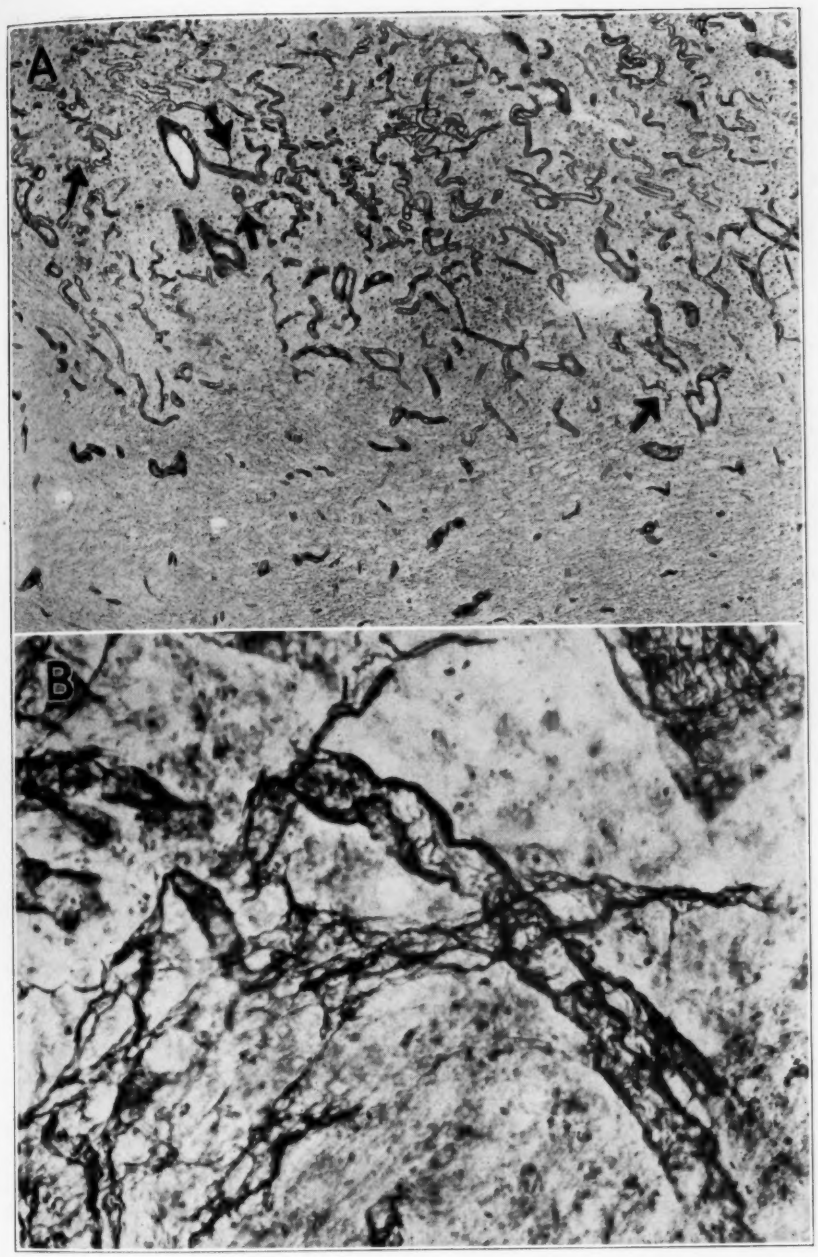

Fig. 7.—*A*, extreme increase in blood vessels, which have a tortuous, serpentine course. The arrows point to a few of the places where overgrowth of reticulin into the ectodermal tissue has occurred. Foot's stain; × about 20. *B*, high power view of the type of proliferation of reticulin invading the parenchyma. Foot's stain; × 330.

liferation of reticulin into the ectodermal tissue. A few such points are marked by arrows. It is only logical to assume new growth of capillaries where evidence of mesodermal proliferation is so unmistakable. Figure 7 *B* shows the character of this growth of reticulin under high power magnification. The strands, some of which are extremely tenuous, show diffuse growth. In this illustration the major part of the growth crosses a capillary practically at right angles, but frequently the strands appear to be directly continuous with the reticulin fibers disclosed in the capillary wall.

The amount of free growth of reticulin is, on the whole, rather slight. The amount seen in figure 7 *A*, indicated by arrows, is somewhat more than would be generally observed in another microscopic field of the same size.

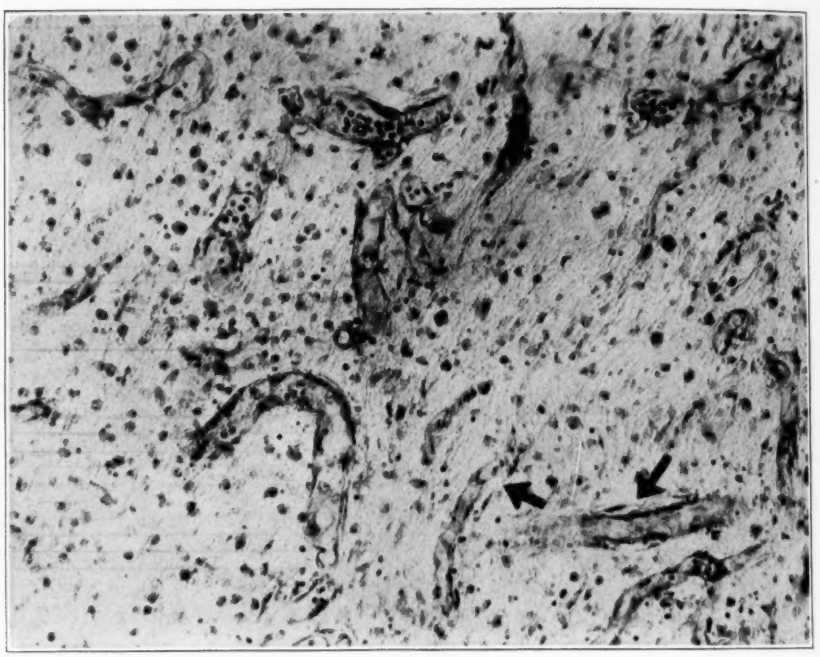

Fig. 8.—Tissue with increased vascularity. The lumens of the larger blood vessels contain many leukocytes. Gitter cells are present in moderate numbers. There are no perivascular infiltration and signs of an inflammatory process. The arrows point to fibroblasts free in the tissue. Thionine stain; × 140.

The appearance of some of the blood vessels stained with thionine is illustrated in figure 8. Most of the vessels in this field happened to be venules. One of the most obvious features was the large number of leukocytes within the lumen of some of the venules. This was a constant feature of practically all the larger blood vessels throughout the lesions and is usually much more marked than is here figured. Red blood cells were rare, while leukocytes might be densely packed together. This was in general restricted to the lesions and was absent from the normal parts of the brain. The crowding of the lumens with leukocytes was not accompanied by inward proliferation of endothelium or reticulin or by

any such signs of thrombus formation. On the significance of this concentration of white blood cells we are not prepared to make any definite statement. In spite of the fact that it was largely restricted to the diseased areas, we do not consider it to be of etiologic significance and regard it as most probably an agonal phenomenon.

There are several other points worthy of mention. We wish to emphasize the complete absence of hematogenous perivascular infiltration. Figures 6 and 8 show numerous gitter cells, which, especially in figure 6, exhibit a tendency to collect in the vascular adventitia. Nevertheless, there are practically no hematogenous cells free in the tissue. Frequently, low power views of a field give the impression that the tissue is heavily spotted with dense masses of leukocytes. These invariably prove to be contained within the lumens of very thin-walled vessels. Leukocytes are not observed outside of the walls of vessels. Occasionally a few small mononuclear cells are to be seen in the vascular adventitia, which may be small lymphocytes, but this identification cannot be made with certainty. Plasma cells have never been observed in the tissue, nor have polymorphonuclear leukocytes. It may also be noted in this connection that, although careful search was made, we have been unable to demonstrate the transition from endothelial cells to phagocytes.

A further feature of the diseased areas was the prominence of the vascular adventitia. There was no sign of a perivascular space in the sense of a preformed fluid-filled pathway of the type seen around cortical blood vessels. But most of the blood vessels, particularly the larger ones, were accompanied by a framework of reticulin and collagen, which, as has already been indicated, tended to invade the nerve tissue in a diffuse manner, without giving evidence of disrupting any pia-glia membrane. No sharp boundary could be drawn between the ectoderm and the mesoderm in thionine preparations. In material impregnated by the method of Foot, for staining reticulin, the boundary is sharp except for the invasion of the parenchyma by reticulin.

These points are made clear by reference again to figure 7 *A* and by examination of figures 8 and 9. In figure 8 several spindle-shaped cells (indicated by arrows) can be seen close to the walls of blood vessels. These spindle-shaped cells we interpret to be fibroblasts. They are to be observed not only around the blood vessels but also as a prominent feature free in the tissue. In figure 9 *A* several such cells can be seen between the two blood vessels included in the illustration, while in figure 9 *B*, under higher power magnification, such a cell is visible very close to the wall of a venule, with another one just to the left, free in the parenchyma.

The identification of these cells as fibroblasts has been made only after long study. The overgrowth of reticulin, as indicated in figure 7, favors this view. In addition, study of the finer morphologic features of these cells, in both Nissl preparations and gold chloride preparations, has shown their identity with young fibroblasts. We have had the opportunity, through the instrumentality of Dr. Frederic Parker Jr., of studying sections of a fibrosarcoma impregnated with silver carbonate by the method of Hortega. Such young fibroblasts seem identical with those in our preparations, whether viewed in thionine or in gold chloride preparations. In both cases the cells are long and bipolar, with occasionally a Y-shaped branching at either extremity. Lateral branches, such as are seen in the microglia cells, or multibranching processes, such as are seen in astrocytes, are not present.

In a recent paper Tuthill and Beck [12] described cells of similar morphologic features, derived from the adventitia, which they called "adventitial wall cells" and which they claimed are transformed into microglia cells. The cells in their illustrations show a marked similarity to our cells, in both morphology and distribution. Their claims, however, that these cells become transformed into microglia cells were not adequately documented. In our own preparations, in which the gitter cells and transitional forms of microglia cells were prominent, we have not been able to find a single case of transformation of a fibroblast into a compound granular corpuscle. In some instances the fibroblasts appeared somewhat blunter and less spindle-shaped than in the illustrations and might have numerous fine vacuoles in their cytoplasm, but they never lost identity as fibroblasts in either their cytoplasmic or their nuclear morphology. We have never seen forms of these cells which resemble the transitional forms of microglia cells. The latter were prominent in our preparations, especially in the lesions in the centrum ovale, where they may be seen in figure 6.

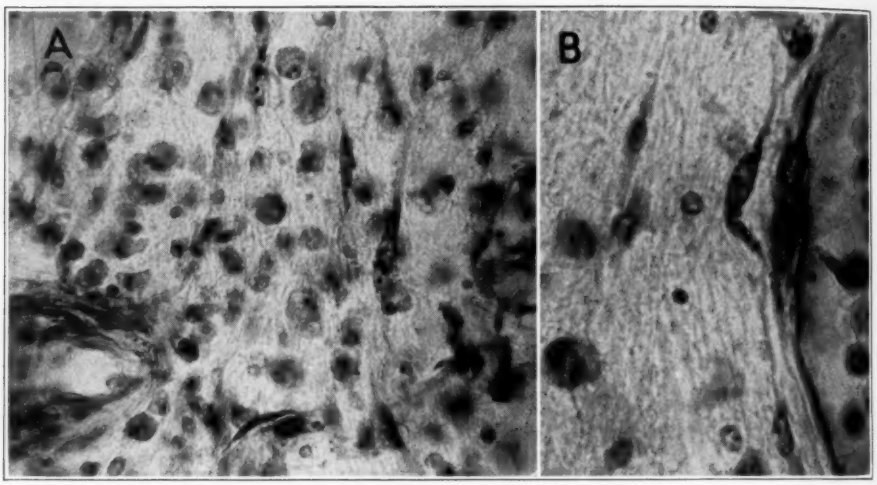

Fig. 9.—*A*, fibroblasts intermingling with other cellular elements free in the tissue. The vessel on the left shows a much thickened adventitia, with accumulations of cells therein. None of these cells, however, are blood elements. Thionine stain; × 400. *B*, two fibroblasts invading the brain tissue. Thionine stain; × 600.

Phagocytic cells, however, do originate from the vascular adventitia. One of us [13] has previously described this process in vitally stained spinal cords of rabbits. In the present case the larger vessels showed large numbers of gitter cells in their sheaths (as shown in figure 9 *A*). Some of these cells were large, fully formed and typical; others were smaller and not fully developed; frequently, mitotic figures were present in such cells, even when they contained considerable lipoid

12. Tuthill, C. R., and Beck, G. M.: Reaction of Cerebral Tissue to Direct Injection of Oil, Arch. Neurol. & Psychiat. **29**:1263 (June) 1933.

13. King, L. S.: Vital Staining of Microglia, Arch. Path. **19**:656 (May) 1935.

material. There was never any confusion, however, between such phagocytes and the fibroblasts. The former had been derived, undoubtedly, from the macrophages preexisting in the adventitia. As was emphasized in a previous communication, it is impossible to differentiate in respect to origin any fully developed gitter cells.

The cortex was carefully studied in the hope of observing changes which would point to the origin or termination of callosal fibers, but this proved to be impossible. In all the areas examined the cyto-architecture was normal. There were no areas of focal loss of cells and no alteration of lamination which we could detect. Staining of axis-cylinders and myelin sheaths did not disclose any abnormality or pathologic alterations.

Slight pathologic changes were present, but these seemed to be essentially independent of the disease process. Some of the large pyramidal cells showed from mild to moderate chromatolysis and eccentricity of the nucleus. This was especially pronounced in the large ganglion cells of the medulla. The neurons contained relatively large amounts of pigment, staining metachromatically green with thionine. Fat stains of the cortex showed a heavy deposit of lipoid pigment within the neurons, far more than would be altogether normal in a healthy man of the patient's age. There was a moderate degree of increase in glial satellites around many neurons, and occasionally active neuronophagia and the presence of glial rosettes could be noted, especially in the deeper layers of the cortex.

The microglia presented moderate progressive changes. Much more cytoplasm was visible in thionine stains than would be considered normal. Numerous fully developed rod cells were present, both in the cortex and in the medullary nuclei. Large amounts of lipoid material were present in glia cells of all three types, usually in the form of from two to four small or medium-sized globules for a given cell. This undoubtedly represented lipoid pigment rather than neutral fat, for the stain was yellow rather than bright red with the sudan III or IV preparation, and much of the material corresponded to greenish-staining pigment in pyroxylin-embedded material stained with thionine.

The blood vessels were essentially normal. A few of the vessels presented a slight accumulation of mononuclear cells in their adventitia, but this was never prominent. The walls of the blood vessels were not thickened, but the adventitia might be. No thrombi were noted. The vascular endothelium and many of the adventitial cells contained large amounts of lipoid material, which was similar to that noted in ganglion cells and glia. There was no proliferation of the intima.

The meninges showed a slight degree of cellular infiltration. This, however, was undoubtedly a sequel to the encephalography to which the patient was subjected.

COMMENT

Of the many interesting features connected with this disease, one of the most striking is its geographic or racial distribution. All the cases so far reported have been in Italians. With the exception of the present case, in which the patient was a man born in Italy, all the autopsies were performed in Italy. There naturally comes to mind the query: Is this a racial disease? In this connection one thinks, of course, of Buerger's disease, which was at one time thought to occur exclusively in Jews but which is now known to occur in non-Jews as well. Marchiafava's disease, so far as is known, has never yet occurred in a non-Italian. This racial distribution must for the present remain an unexplained fact.

It is further noteworthy that all the cases have occurred in males. D'Abundo [14] has reported demyelinization in the corpus callosum in two women, sisters, but since the clinical history and the distribution of the lesion were not at all similar to those in Marchiafava's disease, these two cases cannot be accepted as belonging in the present category. On this point there is agreement among all authors.

Study of the age distribution indicates that the disease occurs in the latter half of life, in the period when the so-called degenerative diseases appear. Undoubtedly, age is an important factor in the etiology. In regard to the age group, Marchiafava's disease differs from other demyelinating processes, such as multiple sclerosis, Schilder's disease or diffuse sclerosis, the disease of Pelizaeus and Merzbacher, acute multiple sclerosis and related conditions which in general seem to affect young adults or even children.

A possible etiologic factor which has received much attention in the literature is alcoholism. Marchiafava and Bignami,[1] in their original description of three cases, entitled their paper "On an Alteration of the Corpus Callosum Observed in Alcoholic Subjects."

All other authors have considered alcohol as a causative agent, but obviously not the only cause. In our case no history of alcoholic intemperance was obtained. On a critical reading of the reports of some of the other cases in the literature it appears that somewhat more emphasis has been placed on chronic alcoholism than the evidence warrants.

When we attempt to evaluate the importance of alcohol, our case with a history of no excessive indulgence is a unique exception. Nevertheless, from the reports in the literature the evidence of severe alcoholism is, on the whole, too striking to be dismissed because of its absence in one instance. We are willing to accept alcoholism as of etiologic importance, although perhaps not to the extent to which previous authors have regarded it. We would suggest an analogy to the undoubted effects of tobacco in relation to Buerger's disease. In both conditions the excessive use of liquor or of tobacco is far more prevalent than the incidence of the disease in question.

The common feature which is present in all the cases of the condition called Marchiafava's disease and the one on which such a designation is based is the presence of symmetrically placed areas of demyelinization in the corpus callosum. It is on this criterion that the cases of D'Abundo are excluded. In all but one case the genu and anterior third of the corpus callosum were constantly affected. The extent of degeneration backward toward the splenium is variable. For

14. D'Abundo, G.: Sopra una particolare neuropatia spasmodica con disturbo del linguaggio articolato, Riv. ital. di neuropat. **10**:233, 1917.

the most part, the areas of degeneration become confluent across the midline; this is always true anteriorly; posteriorly, such areas may remain discrete.

In addition, other symmetrically placed foci of demyelinization are occasionally reported. These are inconstant in distribution, lesions in the anterior commissure being the most constant single observation, while the centrum ovale of each hemisphere is frequently affected but not always in the same place in every case. Symmetrical lesions in the brachium pontis have been reported once. In the present paper, demyelinization in the optic chiasm is reported for the first time.

Microscopic examination was not made in all the cases reported in the literature. In all the cases in which histologic studies have been made, however, the persistence of axis-cylinders in the areas of demyelinization has been reported. Another feature on which there is general agreement is the absence of gliosis. Apparently, localized progressive alterations are possible in small portions of the lesions (the case of Guccione). It is agreed, however, that degenerative changes in the macroglia are the rule.

All the reported cases are similar in regard to a further point: the absence of inflammation. The whole concept of inflammation is at best a field of dispute, and this is doubly true in regard to the nervous system. The participation of mesodermal—that is, blood and connective tissue—elements, is usually regarded as essential. The presence of polymorphonuclear leukocytes is not necessary. The presence of a sufficient number of lymphocytes and plasma cells, in the absence of other mesodermal changes, is usually adequate to warrant a diagnosis of inflammation, either primary or "secondary."

No author has claimed that an inflammatory or encephalitic process is present in Marchiafava's disease. Occasional descriptions may seem slightly inconsistent with this. For example, Marchiafava, Bignami and Nazari,[4] in reporting their series, described an inconstant infiltration of adventitial spaces with "lymphocytoid elements" but gave no indication of how extensive this was. Bignami and Nazari [6] described some lymphocytes in the tissue. The presence of such cells is not a necessary part of the disease picture. Plasma cells have not been observed. From a careful study of the literature in which different cases are described in varying degrees of detail it is our conclusion that the extravascular presence of blood elements is an inconstant and negligible feature in Marchiafava's disease. In our own case long continued search was necessary to detect even a single questionable lymphocyte in the vascular adventitia.

The pathologic anatomy of the blood vessels in the demyelinizing diseases in general is becoming of increasing importance in view of

Putnam's [15] recent work. In the literature on Marchiafava's disease pathologic changes have been described in the blood vessels, but they seem to be of minor importance. "Hyalinization" of walls of the vessel has been reported with moderate frequency, as well as "perivascular hyaline changes." Swelling of the endothelium and thickening of the adventitia have also been reported with moderate frequency. Bignami and Nazari,[6] in their series of thirty-one cases, have observed some diminution of the lumens and evidence of some obliterated vessels. Nevertheless, they expressly stated that the disease is not of vascular origin. Mingazzini,[8] after reviewing all the literature with the exception of the one case of Guccione, together with his own observations on four cases, declared that the hyaline degeneration does not stand in strict relation to the severity and extent of the callosal degeneration. From our own study of the literature it appears that the vascular changes, on the whole, are slight and that most of the vascular changes present in the lesions are also to be seen in normal parts of the brain.

Of further interest in this respect is the mode of spread of the disease. There is agreement in the literature, which has been confirmed by our own observations, that multiple small foci are the earlier lesions, with coalescence as a later development. This would suggest that the involvement begins around the smaller radicles of the vascular tree; that is, the origin of the disease is probably vascular.

Regarding Marchiafava's disease as an example of the demyelinating encephalopathies, we tend, in considering the etiology, to agree with Putnam [16] that the responsible agent is some abnormality in exchange between the contents of the blood stream and the tissues. We do not think that the morphologic alterations visible in the blood vessels under the microscope furnish of themselves an adequate explanation. Consequently we cannot subscribe to any doctrine of mechanical blockade of the vascular system. Neither can we sympathize with the doctrine of a hypothetic toxin. Infection as an explanatory concept has nothing in its favor. We advance no opinion concerning the exact and ultimate pathogenesis. Yet we definitely commit ourselves to the generality already enunciated that the disease process is related in some way, as yet unknown, to the vascular system.

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15. Putnam, T. J.: Personal communication to the authors, 1935; Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929 (May) 1935; VII. Similarity Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, ibid. **35**:1289 (June) 1936; Etiologic Factors in Multiple Sclerosis, Ann. Int. Med. **9**:854 (Jan.) 1936.

16. Putnam, T. J.: Personal communication to the authors.

VASCULAR CHANGES IN THE LATERAL GENICULATE BODY FOLLOWING EXTIRPATION OF THE VISUAL CORTEX

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CHICAGO

Wounds, foreign bodies, dead cells and other injurious agents usually induce reactions in a bodily tissue in which blood vessels with their contents play a leading rôle. Small blood vessels, including capillaries, are dilated and have an increased flow of blood. The permeability of the walls of the vessels is heightened, so that liquid from the blood penetrates the crevices of the surrounding tissue and leukocytes pass through the endothelial wall and approach—together with histogenous wandering cells—the affected region. Capillaries increase in number through "budding." All these changes imply a "protective" and "defense" mechanism to clear the site of injury and start repair.[1] This holds in a different degree for all kinds of bodily tissues.

Some neurologists (von Monakow,[2] Campbell[3] and others) consider that the brain tissue is an outstanding exception to this general rule. The disturbing effect of an injury to the brain is supposed to reach far beyond its site owing to the interruption of the blood supply to adjacent or even remote parts. The reason for such a view is probably the false belief that "there is no anastomosis between the smallest arteries of the brain. If one of these is obstructed, there is no further possibility of reestablishing the circulation, and the part of the nervous system supplied by the affected vessel undergoes degenerative changes.[4]

I have shown elsewhere experimentally that the vascularity is normal or supernormal in and around a lesion in the cerebral cortex of the rat.[5] The increased vascularization, when present, manifests itself in

From the psychologic laboratory, the University of Chicago.

1. MacCallum, W. G.: Text-Book of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

2. von Monakow, C.: Gehirnpathologie, ed. 2, Vienna, Hölder-Pichler-Tempsky, 1905.

3. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, London, Cambridge University Press, 1905.

4. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1923.

5. Tsang, Y. C.: Vascular Changes Following Experimental Lesions in the Cerebral Cortex, Arch. Neurol. & Psychiat. **35**:1280 (June) 1936.

one or more of the following changes: increase in the number of blood vessels, enlargement of their caliber and thickening of the capillary anastomosis. Moreover, the small arteries of the brain certainly do anastomose with each other.[6] I noticed that the terminal arteries, when cut off from the main trunk, may change their affiliation and become functionally associated with other blood vessels. In short, the vascularity of the injured brain tissue tends to be increased in harmony with the general rule already mentioned.

Pathologic changes in nerve tissue may also occur at points remote from the primary lesion as a result of degenerative changes in nerve fibers or the retrograde degeneration of nerve cells. These changes are pronounced in the thalamic nuclei after the destruction of the cortical areas to which their centripetal fibers are projected. After the destruction of the striate areas in rats, for example, the ganglion cells of the lateral geniculate body undergo degeneration and eventually complete disintegration. In addition to this, there is a marked increase in the number of glia cells and in many cases a heavy infiltration with leukocytes, with eventual breaking down of the tissue and the formation of a cyst in the center of the nucleus. These changes are observable in practically all rats which have been kept under observation for several months after operation on the cortex. There is no indication of infection, and the changes are restricted to the thalamic nuclei the projection tracts of which have been destroyed.

What is the condition of the vascular system in these degenerating areas? Does the cellular degeneration induce vascular changes? Is the gliosis or final disorganization of the tissue referable to vascular changes? Some clue to the part played by the vascular system in the production of the pathologic phenomena of retrograde or secondary degeneration can be obtained by direct study of the blood vessels at the site of degenerative processes.

With this problem in view, I have undertaken a study of the vascular changes in the lateral geniculate body after destruction of the striate area of the cerebral cortex. The striate area was first destroyed, and a contrast medium was later injected into the blood vessels of the brain. In order to see whether anything happens to the vascular system of the lateral geniculate body when centripetal impulses from the end-organ are eliminated, three rats were blinded unilaterally by enucleation of the right eye. The same medium was injected into the brains afterward.

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6. Pfeiffer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928; Grundlegende Untersuchungen für die Angioarchitektonik des menschlichen Hirns, Berlin, Julius Springer, 1930.

METHODS

Thirteen albino and hooded rats were used. They were adults at the time of operation, except rat 8, which was operated on on the twenty-second day. This animal was used for a study of the effects of hemidecortication in infancy. With the rats under ether anesthesia, and with aseptic precautions, the visual area was destroyed with electric thermocautery or a wire. The lesion was made in one hemisphere, except in rats 8, 9 and 10, which were deprived of both visual areas. The lesion was generally larger than the strictly visual cortex, the striate area (fig. 1). Under similar conditions the right eyes of rats 11, 12 and 13 were enucleated. The animals after operation lived under sanitary laboratory conditions until the time of vascular injection.

The time between operation and injection ranged from eleven to one hundred and fifty-three days. With the animal under ether anesthesia a cannula connected

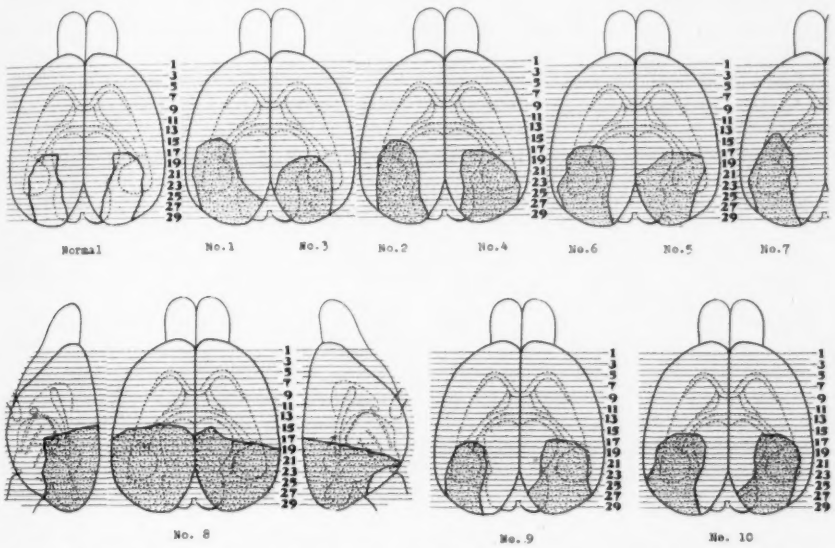

Fig. 1.—Reconstructions of the cortical lesions in the experimental animals. The shaded area marks the extent of the injury. The lesions are generally much larger than the normal striate area shown in the first reconstruction. The normal area is a composite picture of two mappings on the basis of two normal series of sections stained by the Nissl method.

with the injection apparatus was inserted into the ascending aorta. After the blood vessels of the brain had been washed out by the preparatory injection of physiologic solution of sodium chloride, Bensley's carmine and gelatin mixture was injected by means of a pressure bottle. A cord was passed around the aorta and tied. The head was then cut off and dropped into a dilute solution of formaldehyde U. S. P. (1:10) to fix the brain in situ.

The brain was then prepared for sectioning. Pyroxylin sections 120 and 40 microns thick were cut alternately and mounted on separate slides, so that sections occupying identical positions on the two slides were neighbors. The thick sections were stained lightly with thionine, while the thin ones were stained deeply for cells. The sections were finally cleared in xylene and mounted in balsam.

The thick sections showed the vascular condition of the lateral geniculate body, and the thin ones, the condition of the cellular mass. For a qualitative study with the injection technic, the thicker the section (within a certain limit) the less the chance of misjudgment.

On the basis of representative sections at definite intervals, the cortical lesion was reconstructed on Lashley's diagram of the rat's cerebrum (fig. 1). Only the dorsal view of the lesion is shown, except in rat 8, in which the lesion was more extensive.

EXPERIMENTAL DATA

Individual protocols were kept for the experimental animals, a summary of which is given in the accompanying table. In most cases the lesion was confined to one hemisphere. Thus, the vascular condition of the lateral geniculate body on the normal side serves as a criterion of comparison. The affected lateral geniculate bodies of rats 8, 9 and 10, in which bilateral lesions were made, were compared with the corresponding normal structures of other animals in which the results of injection were satisfactory. On the whole, the injection of the contrast medium into the blood vessels of the brain was successful.

Individual Records of the Experimental Animals *

Rat No.	Variety	Weight at Necropsy, Gm.	Operation	Date of Operation	Date of Injection	Time Interval, Days	Vascularity of C. G. L.
1	Albino	150.5	L	July 3	July 13	11	+ (?)
2	Black hooded	235.7	L	March 31	May 3	34	++
3	Albino	174.6	R	May 25	June 29	36	+
4	Black hooded	227.2	R	April 20	June 28	70	+
5	Albino	227.2	R	April 14	June 23	71	+
6	Albino	178.9	L	April 20	July 7	79	++
7	Albino	213.0	L	April 15	July 7	84	++
8	Black hooded	221.5	LR	March 25	July 11	109	+ (?)
9	Hooded	264.1	LR	Feb. 8	June 28	141	+
10	Black hooded	249.9	LR	Feb. 4	July 6	153	++
11	Albino	150.5	R eye	July 3	July 13	11	(?)
12	Black hooded	227.2	R eye	May 25	June 27	34	(?)
13	Hooded	264.1	R eye	March 31	July 6	98	(?)

* Rats 1 to 10 were deprived of the visual area of the cerebral cortex; L means the left and R the right side. Rats 11 to 13 were blinded by enucleation of the right eye. All the dates refer to the year 1935. "Time interval" is the number of days between operation and injection. In the last column the vascularity of the corpus geniculatum laterale (C. G. L.) is indicated by + in case of an increase or by ? in case of no definite change recognizable.

RESULTS

With the possible exception of the brains of rats 1 and 8, in which the injections were not satisfactory, all the specimens showed unquestionable increase of vascularization in the dorsal nucleus of the lateral geniculate body on the affected side. This was evidenced by an enlargement of the afferent vessels, an increase in their number and an enrichment of the capillary network. The permeability of the walls of the vessels seemed also to be heightened, so that diffusion of carmine was noticed in practically all the specimens. Such changes invariably followed

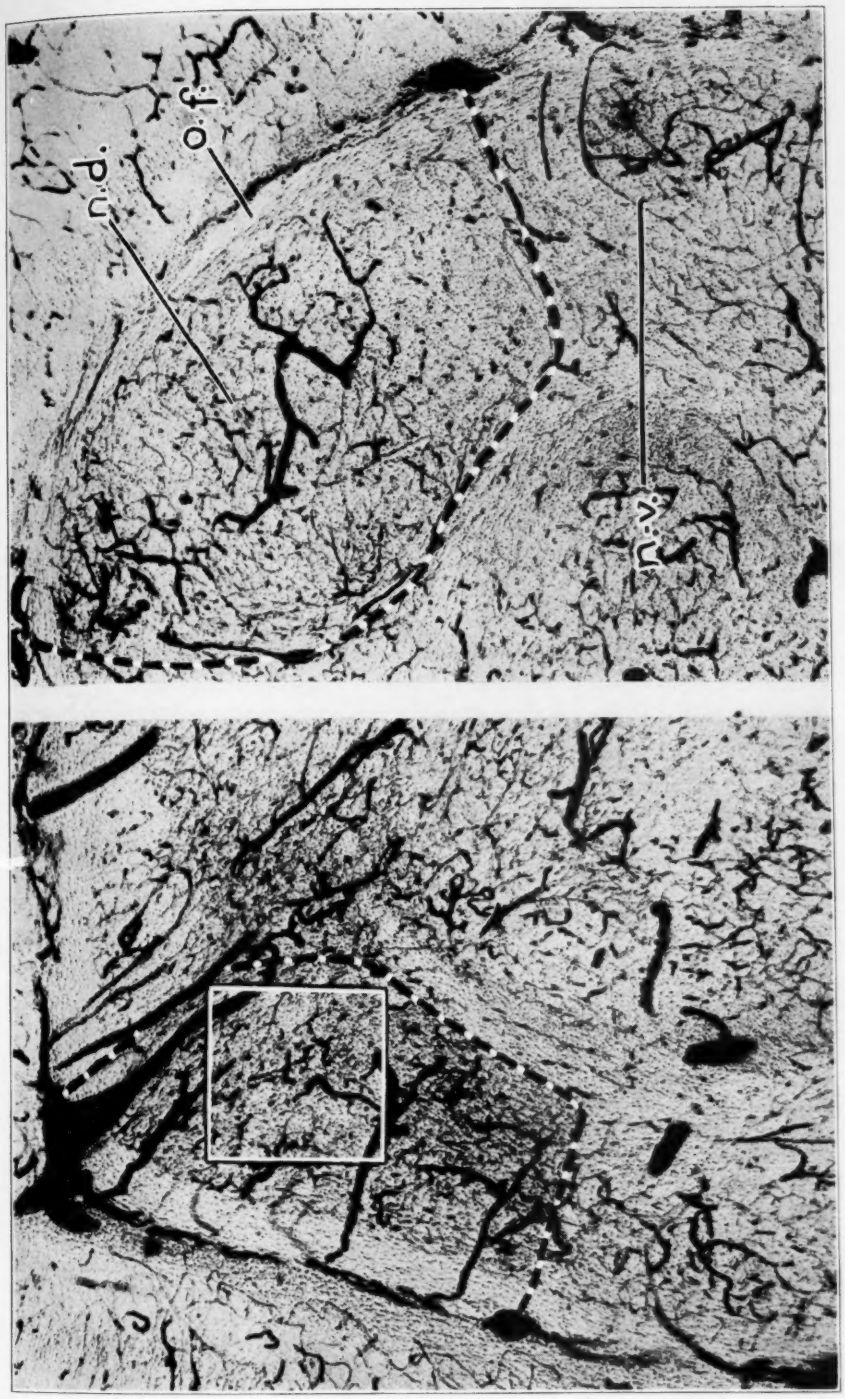

Fig. 2.—Photomicrographs of the dorsal nuclei of the lateral geniculate bodies in one section taken from rat 6. The two pictures are of the same magnification (× 75). The heavy dashes mark the medial and ventral boundaries of the dorsal nucleus. The affected (left) nucleus is shrunken in size as a consequence of the secondary degeneration. The square in the left nucleus marks the area in which the capillaries have been traced under the projection lens (shown in figure 3). The capillaries are poorly represented in the photomicrograph; they contribute partly to the dark hue of the background. The carmine and gelatin mixture was used for injection. The nucleus dorsalis is indicated by *n. d.*; the nucleus ventralis, by *n. v.* and the optic fibers, by *o. f.*

destruction of the visual area on the same side, irrespective of the size of the lesion, the location of the injuries in one or both hemispheres and the length of time between operation and injection.

Figure 2 shows the lateral geniculate bodies in one section taken from rat 6. The visual area of the left hemisphere was removed, and the degenerative influence was on the lateral geniculate body on that side. Here the contrast in vascularity between the normal and the affected side is certainly sharp. The afferent vessels are greatly increased in caliber. Some come in directly from the anterior or middle branch of the posterior cerebral artery.[7] Vessels of such enormous caliber are never seen in a normal structure. The number as well as the size of such afferent vessels is apparently increased. The capillaries form a dense mass, contributing to the reddish hue (dark in the photomicrographs) of the background. Figure 3 shows the camera tracings of the capillaries in a small area (marked by the square) within the lateral geniculate body, reproduced in figure 2. The

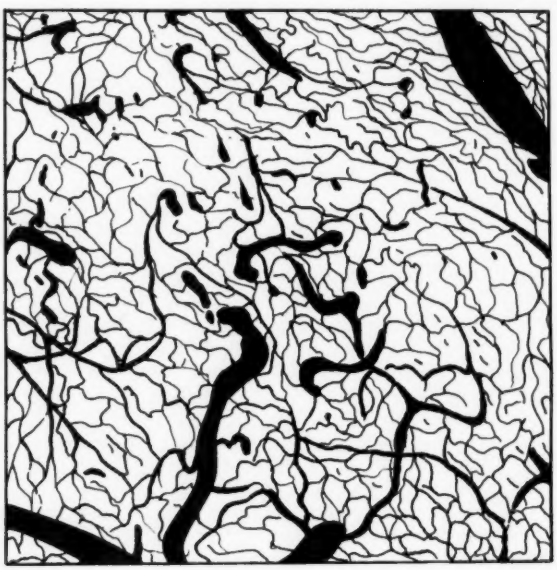

Fig. 3.—Camera tracings of the blood vessels in the square marked out in the left nucleus in figure 2 (× 250). The carmine and gelatin mixture was used for injection.

finest capillaries are not easily revealed by photomicrography. Diffusion of carmine through the vessels to the ground substance is mainly responsible for the dark hue of the background.

In most of the animals in which the cortex was operated on the general tendency toward heightening of vascularization in the affected lateral geniculate body was unmistakable, but the contrast between the affected and the normal structures presented all possible degrees of sharpness. The very nature of such a study forces one to call special attention to the animals in which the injection was more successful, i. e., rats 2, 6, 7 and 10.

7. Tsang, Y. C.: The Blood Supply of the Lateral Geniculate Body in the Rat, J. Comp. Neurol. **61**:553 (June) 1935.

In animals in which small lesions were produced, the vascular changes were confined within the dorsal nucleus of the lateral geniculate body and the immediate neighborhood. In those in which the injury was extensive, the effect spread to other parts of the thalamus, e. g., the lateral nucleus and habenular nucleus. It should be emphasized that the increase in vascularization was never recognized in the ventral nucleus of the lateral geniculate body (fig. 2). This is in harmony with the generally acknowledged view that the cells in the ventral nucleus do not send ascending fibers to the cortex.

The darkly stained cyst in the affected lateral geniculate body in rats 4, 7 and 9 was mentioned in a former paragraph. Under high power magnification, the cyst appears as a cluster of transparent vacuoles surrounded by numerous glia cells and probably wandering cells. Capillaries wind in and around the cyst, but they apparently had nothing to do with its formation. No trace of hemorrhage is recognizable. The heightened permeability of the vessels and the perivascular infiltration can hardly be related to it directly. The cyst could not be the result of postoperative infection, for it was deeply embedded in the gray mass, not in direct communication with the lesion or with the lateral and outer surface of the lateral geniculate body. After a careful examination of such specimens in this and in other studies, I am reasonably sure that the transparent vacuoles are adipose droplets formed after the decomposition of the myelin sheath of the optic radiation fibers. Sometimes the droplets are merely scattered in the affected region and do not accumulate into a cluster. In such a case few or no glia cells are attracted to their side. Such scattered droplets were found in rat 8. At other times the cluster consists of a few droplets. It is only when the accumulation of lipoid attains a considerable size, surrounded by glia cells and probably wandering cells, that it reflects strongly the color of the stain. Such pathologic changes, called nodules or granulomas, are fairly common in the large group of inflammatory diseases of the central nervous system.[8] However, it is remarkable for such a condition to occur in a region that is merely undergoing secondary degeneration.

It should be mentioned in passing that from eleven to ninety-eight days after enucleation of the right eye the more affected lateral geniculate body, on the left side, showed no changes in the vascular system. It is conceivable that some reaction may have been set up in that region as a consequence of degeneration of the optic fibers, but the reaction was too weak to be reflected in vascular changes.

COMMENT

Retrograde degeneration in the dorsal nucleus of the lateral geniculate body after homolateral destruction of the visual area throws that nucleus into a state of local tissue reaction in which the blood vessels with their contents play a major rôle, just as in other tissues in a similar state. The enlarged caliber of vessels, the heightened permeability of their walls, the increase in the number of vessels and the enriched network of capillaries are interpreted as measures to increase the flow of blood for clearing and antagonizing the noxious débris.

There is no question concerning the enlargement of the afferent vessels and the heightening of their permeability. The formation of

8. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, Baltimore, William Wood & Company, 1933.

new feeding vessels in postnatal life may seem questionable. The apparent proliferation of such vessels may be partly explicable by widening of the preexisting smaller vessels. The possibility still remains, however, that arteries and veins may be formed from capillaries, and larger vessels from smaller ones.[9] In fact, the proliferation of blood vessels is not infrequently met with in inflammatory diseases of the nervous system.[8]

Some authors are skeptical as to the postnatal proliferation of capillaries in the nervous system, although it is a common occurrence in other kinds of tissues in pathologic states. In normal brain tissue only a part of the total capillaries are distended with the circulating injection medium, others being in a collapsed condition. The increased flow of blood and the widening of the vascular caliber under the degenerative influence may permit injection of a contrast medium into the otherwise collapsed capillaries, thus presenting a picture of apparent increase in number. Furthermore, consequent to the degeneration and subsequent vanishing of ganglion cells in the lateral geniculate body, the capillaries come naturally closer together and give an appearance of heightened density. However, apart from all these probabilities there seems to be a genuine increase of capillaries in my specimens in which the injection was successful. In a previous study I made a small undercut in the visual cortex of the rat with a needle.[5] Minute bits of scar tissue were seen in that region, but no disturbance of cell lamination was recognizable. I found a thick skein of finest capillaries winding in and around the minute scars. The density of the capillaries was such as I had never observed in normal tissues, however satisfactory the injection. Thus, the formation of new capillaries through "budding" from preexisting ones seems to be a fact even in the central nervous system.

Another interesting feature is the long duration of the increased vascularization in the affected part. One hundred and fifty-three days (rat 10) after the operation the lateral geniculate body was still highly vascularized. The vascular changes in inflammatory states in other tissues are usually temporary.[10] After a certain period the circulatory system is restored to a normal condition. The long duration of the high vascularization may be partly attributed to the slow and prolonged process of the secondary degeneration. However, the ganglion cells are apparently degenerated completely long before one hundred and fifty-three days. The affected dorsal nucleus of the lateral geniculate body presents a picture of "chronic inflammation."

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9. Maximow, A. A., and Bloom, W.: Text-Book of Histology, ed. 1, Philadelphia, W. B. Saunders Company, 1930. Pfeiffer.[6] Hassin.[8]

10. Hassin.[8] MacCallum.[1]

The proliferation of the neuroglia cells in the degenerating lateral geniculate body is concomitant with the vascular changes. After destruction of the striate area the glia cells multiply rapidly in the dorsal nucleus of the lateral geniculate body. In a few weeks the last images of the "ghosts" of the degenerated ganglion cells vanish from the scene, leaving a thick layer of glia cells. The glia cells, like certain wandering tissue cells, seem to be capable of protective response against invasion. Under the degenerative influence the glia cells return to an embryonic condition, proliferating rapidly and indefinitely at the site of degeneration. It seems safe to say that the vascular changes and gliosis in the lateral geniculate body undergoing secondary degeneration are concomitant phenomena; it is not known whether they are causally related.

SUMMARY

The visual area of the cerebral cortex in ten rats was removed, in seven on one side. In from eleven to one hundred and fifty-three days after the operation a mixture of carmine and gelatin was injected into the blood vessels of the brain of each animal. Three rats were deprived of the right eye, and the same mixture was injected into the brain after from eleven to ninety-eight days. The lateral geniculate body was examined microscopically with the following results:

In the dorsal nucleus of the lateral geniculate body on the side of the lesion the vascularity was increased in most cases. This was manifested by enlargement of the afferent vessels, apparent increase in their number and thickening of the capillary network. The permeability of the vessels was also heightened, so that free diffusion of carmine into adjacent tissues was recognized in almost all cases.

The vascular changes just mentioned seemed to be independent of the size of the lesion, the location of the injury in one or both hemispheres and the length of the period of degeneration from eleven to one hundred and fifty-three days.

In animals in which the lesion was extensive the vascular changes spread to other parts of the thalamus which presumably have fiber connections with the parts destroyed. Such changes never occurred in the ventral nucleus of the lateral geniculate body.

In from eleven to ninety-eight days after enucleation of one eye no noticeable vascular changes were found in the lateral geniculate body on the same or opposite side.

CEREBRAL FRONTAL AGENESIS IN ASSOCIATION WITH EPILEPSY

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CINCINNATI

Changes in 178 brains of persons who had had convulsions are reviewed. Gross pathologic change was demonstrated in 174 of the brains and anomalous blood vessels in 2, and 2 were considered to be normal. In 34 cases in the series a clinical diagnosis other than idiopathic epilepsy was made and substantiated. In this group of cases the following clinical and pathologic conditions were observed: tumor of the brain, in 1 case; syphilitic meningo-encephalitis, in 6 cases; meningitis (all types), in 21 cases; traumatic encephalitis, in 2 cases; encephalitis, in 3 cases, and alcoholism, in 1 case.

A diagnosis of epilepsy with some degree of amentia or dementia was made in the remaining 146 cases. In this group of cases of idiopathic epilepsy in which no clinical diagnosis was made, the pathologic observations were as follows:

Condition	No. of Cases
Unilateral cerebral agenesis	4
Unilateral frontal atrophy	4
Bilateral frontal atrophy	60
Atrophy of the temporal lobe	2
Atrophy of the occipital lobe	3
Generalized cortical atrophy	3
Cystic choroid plexus	15
Tumor of the choroid plexus	3
Dilatation of the ventricles	9
Cerebral edema	8
Atheromatous vessels	5
Chronic thickening of the meninges	8
Unilateral predominance of pacchionian bodies	4
Hyperplasia of pacchionian bodies	6
Venous engorgement	52
Adhesive arachnoiditis	2
Hemorrhage	6
Absence of falx cerebri (frontal)	3
Closed foramina of Luschka	8
Tumor of the frontal lobe	2
Tumor of the occipital lobe	1
Gumma of the parietal lobe	1

Read before the Section on Convulsive Disorders at the Ninety-First Annual Meeting of the American Psychiatric Association, Washington, D. C., May 13-17, 1935.

In the group of 146 cases of idiopathic epilepsy, the cause of the convulsions was not determined before death in a single instance. The postmortem observations, in turn, added little to explain the convulsion. There were, however, a number of pathologic changes which warrant discussion, since they were obviously predominant in this material.

These cases fall into three distinct groups, according to the age at onset and the pathologic changes: (1) cases (66) in which convulsions occurred before and near the age of puberty, in association with cerebral frontal agenesis; (2) cases (76) in which convulsions occurred near and after the age of puberty, in association with gross structural disease of

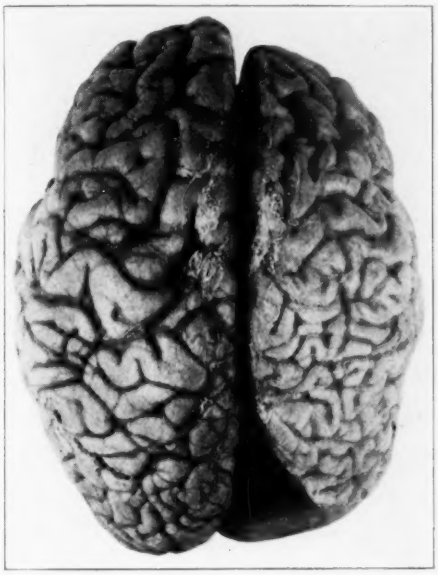

Fig. 1.—Photograph showing partial agenesis of the right cerebral hemisphere, with enlargement of the right cerebellum. The usual arrangement of the gyri is observed on the right side. In the premotor area of the right midfrontal convolution the sulci are wide and deep, and the gyri are proportionately smaller than the adjacent frontal gyri. This is a more localized area of agenesis in the greatly underdeveloped hemisphere.

the brain but not with cerebral frontal agenesis, and (3) cases (34) in which convulsions occurred in association with active organic disease of the brain, all ages.

In group 1 there were 60 cases in which onset of convulsions occurred before the age of 12 years (the arbitrary period of pubescence). In 2 of the remaining 6 cases isolated frontal atrophy was shown, in which the onset was at 13 years of age, in 2, at 14, in 1, at 15 and in 1, at 18, with generalized hemiatrophy or agenesis on the right side (fig. 1).

In 4 cases in this group there was an isolated area of atrophy between the falx cerebri and the anterior cerebral vein (fig. 2). The usual compensatory dilatation of the ventricular system was not observed in these cases. The conspicuous microgyria was present in the areas of agenesis, and the underlying subcortical parenchyma was uniformly decreased (fig. 3).

In group 2 there were 68 cases in which onset of convulsions occurred after the arbitrary period of pubescence. The condition in all the instances was not diagnosed; i. e., it was classified as idiopathic epilepsy. The most common pathologic observations were changes in the cerebrospinal fluid and vascular systems, i. e., changes in the ventricles, meninges, choroid plexus, pacchionian bodies and blood

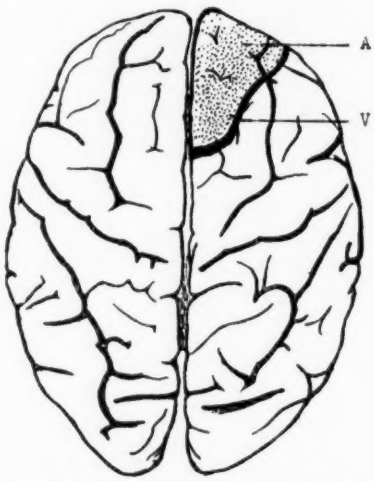

Fig. 2.—Drawing showing an isolated area of atrophy between the falx cerebri and the anterior cerebral vein. *A* represents the atrophic area and *V* the anterior cerebral vein.

vessels. Some of these changes were structural developmental defects, but the majority were the result of inflammatory insults to the cerebrospinal circulatory mechanism. In 38 brains the cerebral veins were greatly distended over the lateral and anterior surfaces of the hemisphere. In all these cases the brain was removed last at autopsy. In 12 brains the venous engorgement was present along the superficial middle cerebral vein, involving the great anterior anastomotic vein of Trolard. Generalized venous engorgement was not observed in the brains of patients who died in status epilepticus but instead was seen to be localized over either one or both frontoparietal areas or in the area of the sylvian fissure. Venous engorgement was noted in the occipital area and around the cerebellum in only 2 brains. In a group of 8 cases there were rather striking correlations: In all instances the onset of

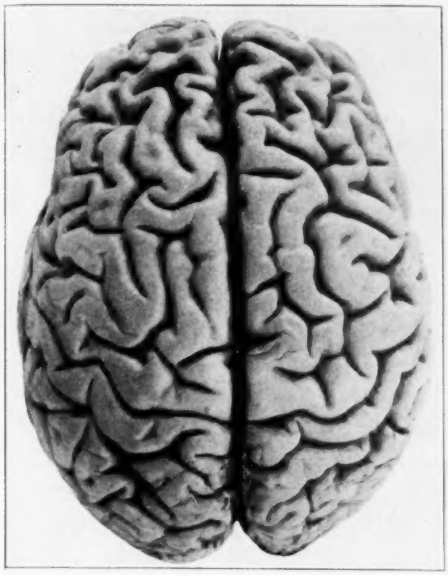

Fig. 3.—Photograph showing bilateral cerebral frontal agenesis in the brain of a young adult in whom convulsions started before puberty. The narrow gyri and the wide and deep sulci in the frontal area are evident.

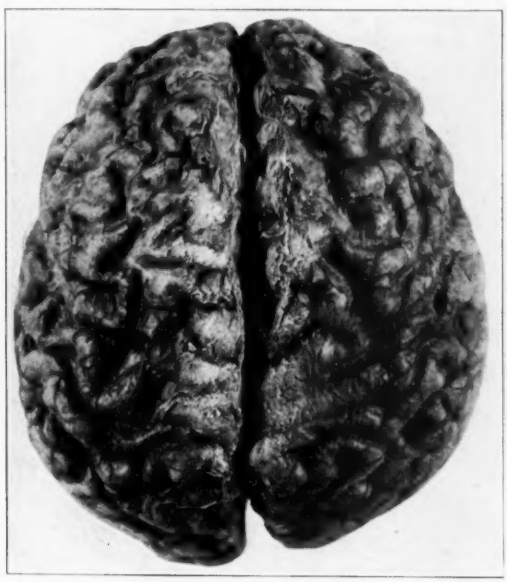

Fig. 4.—Photograph showing generalized cortical atrophy in the brain of a patient with syphilitic meningo-encephalitis. The narrowed gyri and the widened sulci are uniformly present.

convulsions was at the age of 12; not a single brain showed atrophy, but instead 6 presented definite cerebral edema, with dilatation of the ventricles in 4 and congestion of the cortex and chronic arachnoiditis in the other 2.

In the cases in group 3 cerebral frontal agenesis was not present. Frontal atrophy was not observed except in 4 cases of syphilitic meningo-encephalitis, and in these instances it was associated with atrophy elsewhere (fig. 4). For the most part this group of cases in which a clinical diagnosis was made consisted of instances of acute and chronic inflammatory disease. In 9 cases of meningitis in which the exudate was limited to the vertex convulsions occurred early in the disease. In 5 cases the convulsion was a late manfestation in the clinical course, when the exudate became heavy and occluded the pacchionian bodies. In 7 cases of meningitis in which the exudate was primarily at the base the convulsions appeared late in the clinical course; in these brains chronically thickened meninges had obliterated the natural pathway for the cerebrospinal fluid. In these cases of cortical meningitis, the parietal lobe and posterior portion of the frontal lobe of the brain were most involved. The greatest amount of exudate was observed around the largest arachnoidal cell nests. Complete occlusion of some of the pacchionian bodies could be demonstrated in the brains with marked cortical exudate.

COMMENT

It is evident that the pathologic changes presented are not alone sufficient to explain the production of convulsions; if the lesions themselves caused convulsions the patient would be in a chronic convulsive state from the onset of the disease until death. This, of course, does occur, but it is very uncommon. The anatomic changes are considered to be a fundamental, not a precipitating, factor. The precipitating factors are numerous, producing disturbance in the cerebral physiologic function, which alters the threshold for convulsions. Many of the aforementioned structural changes may be observed at autopsy in persons with no history of convulsions. In the absence of precipitating factors even gross changes within the brain may fail to cause convulsions because the lowered threshold for convulsions is not crossed by an appropriate stimulus. Obviously, all this material cannot be described in detail.

Atrophy of the frontal lobe has been the subject of much discussion. This material suggests that in a high percentage of cases so-called cortical atrophy is really cerebral cortical agenesis, particularly when the atrophy is of the frontal portion of the cortex, which is the latest development of the neopallium. In the brains of persons with a history of convulsions which developed after the period of pubescence, the fre-

quency of atrophy of the frontal lobe was no greater than that in a control series of brains of patients with psychosis,[1] while in 60 cases in group 1 of this series onset before 12 years of age and cerebral agenesis were shown. In fact, if the arbitrary age of pubescence were raised to 15, in not one of these cases would there appear isolated atrophy of the frontal lobe, unassociated with other gross anatomic defects. Moreover, in the brains of patients with the late-developing syndrome, atrophy of the frontal lobe alone is not as common as in the brains of patients with psychosis or in those of the ordinary population of the dissecting room. In the cases of this group of young patients with the idiopathic epileptic syndrome, the term atrophy of the frontal lobe should be supplanted by that of agenesis of the frontal lobe.

In the atrophic brain there is compensatory dilatation of the ventricular system. This mechanical adaptive reconstruction in the closed cerebral box has been known for many years and has been previously described.[1a] In the brains of the group of patients with idiopathic epilepsy, with onset before puberty, even marked cerebral frontal agenesis was not accompanied by corresponding enlargement of the ventricular system. This seems to favor the diagnosis of agenesis, since the subcortical structures as well showed underdevelopment and not atrophy.

The irregular distribution of cellular loss in the frontal area favors the diagnosis of agenesis rather than that of ischemic atrophy, as described by Fay.[2] Fay wondered why "one cell suffers more than its neighbor, presumably under the same onslaughts of pressure." He also stated that ischemic atrophy does not occur in other parts of the brain. Since the cranial cavity is an almost closed system, one would expect the effects of pressure to show as generalized atrophy and not as selectivity for tissue of the frontal lobe. To support the contention that pressure atrophy over the frontal lobe is due to accumulation of fluid, it has been demonstrated by Winkelman and Fay[3] that the orbital part of the

1. Bateman, J. Fremont: (*a*) Closed Foramina of Luschka in the Brains of the Insane: Their Influence on the Pathogenesis of the Psychoses, Arch. Neurol. & Psychiat. **14**:616 (Nov.) 1925; (*b*) Obstructions in the Pathway of the Cerebro-Spinal Fluid, Proceedings of the Fifth Annual Convention of the Central Neuropsychiatric Association of Ohio, Cincinnati, October 1926; (*c*) Meningitis with Special Reference to the Rôle of the Pacchionian Bodies, Ohio State M. J. **25**: 970 (Dec.) 1929.

2. Fay, Temple: (*a*) Epilepsy: Clinical Observations on the Control of Convulsive Seizures by Means of Dehydration, J. Nerv. & Ment. Dis. **71**:481 (May) 1930; (*b*) Generalized Pressure Atrophy of the Brain, Secondary to Traumatic and Pathologic Involvement of Pacchionian Bodies, J. A. M. A. **94**: 245 (Jan. 25) 1930.

3. Winkelman, N. W., and Fay, Temple: The Pacchionian System: Histologic and Pathologic Changes with Particular Reference to the Idiopathic and Symptomatic Convulsive States, Arch. Neurol. & Psychiat. **23**:44 (Jan.) 1930.

frontal lobe does not show atrophy. In brains showing frontal agenesis one would not expect the orbital gyri to show atrophy, since they are phylogenetically and anatomically different from the other frontal convolutions. They are connected with the occipital and the inferior temporal cortex by the inferior longitudinal fasciculus. This is a much older, more complex basic mechanism, with its connections, than the middle and superior frontal convolutions. In the brain of the orang-utan and in that of man the orbital operculum is developed behind the fronto-orbital sulcus (Papez [4]). Above the orbital margin the superior and middle frontal gyri are limited in the human brain by a new fronto-marginal sulcus. The anterior and superior parts of the frontal lobe are the most recent and extensive developments of the neopallium. For this reason alone, one might expect cerebral agenesis in these phylogenetically infant parts.

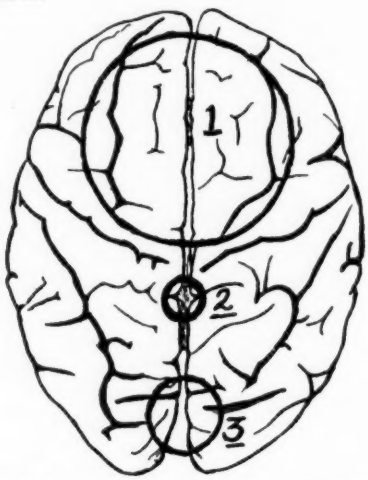

Fig. 5.—Diagrammatic drawing showing the proportionate incidence of atrophy of various portions of the brain of patients with idiopathic epilepsy. Atrophy of the parietal area, represented by circle *2*, is rarely observed unless in association with atrophy elsewhere; atrophy is most common in the area indicated by *1*.

Atrophy alone does not explain the altered threshold for convulsions. In patients with senile dementia atrophy of the brain is conspicuous, but convulsions are noticeably absent. Sufficient anatomic data are not available in cases of syphilitic meningo-encephalitis to show that atrophy or exudate per se is the factor which precipitates the convulsion of dementia paralytica. Certainly, the hyperplastic pacchionian body, as described by Winkelman and Fay,[3] is not the trigger mechanism, for hyperplasia of the arachnoidal granulations is common in apparently

4. Papez, James W.: Comparative Neurology: A Manual and Text for the Study of the Nervous System of Vertebrates, New York, Thomas Y. Crowell Company, 1929.

normal persons (without nervous or mental disease) after the fourth decade of life. However, if one considers the inefficient pacchionian system as subserving a part in the mechanism of production of atrophy, one would expect more marked atrophy in the areas designated as *1* and *3* in figure 5, and this is what occurs. Localized atrophy in the parietal region, designated as area *2*, is very rare, and it is here that the pacchionian bodies are most numerous.

In the examination of 1,900 brains I have never seen evidence of gross atrophy limited to the parietal area, especially along the superior parietal convolution. One commonly sees atrophy in the parietal area, however, associated with generalized cortical atrophy in the brain of a person with dementia paralytica of long standing and in the senile brain. One may conclude, then, that the localized frontal atrophy which occurs in the very young and is associated with the convulsion syndrome is atrophy of a different type from that which occurs in the senile brain. If it is pressure atrophy due to ischemia, as described by Fay,[2b] one must search for the cause of this selectivity or vulnerability of the frontal lobe.

SUMMARY AND CONCLUSIONS

The clinical and pathologic data in a series of 178 brains of persons with convulsions are reviewed.

Cerebral frontal agenesis seems to be the most predominant and charcteristic pathologic condition in the brains of patients with idiopathic epilepsy onset of whose symptoms occurred before or during the period of pubescence.

In the brains of patients with idiopathic epilepsy developing after puberty the frequency of atrophy of the frontal lobe was no greater than in a series of brains of persons with psychosis, used as controls.

Cases of isolated frontal atrophy due to pressure and ischemia were not observed in this series.

OSCILLOPSIA

A NEW SYMPTOM COMMONLY OCCURRING IN MULTIPLE SCLEROSIS

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A symptom which appears not to have been previously described was observed in a recent study of sixty-two cases of multiple sclerosis.[1] It is common in multiple sclerosis, and yet the first person in whom it was noted and who came to autopsy did not have multiple sclerosis but another disease. The name oscillopsia is suggested for the symptom.

Oscillopsia means, literally, oscillating vision. The patient complains that objects seem to move back and forth, to jerk or to wiggle. The oscillation usually occurs only during walking, although occasionally it also manifests itself during fixation of gaze at rest. Most commonly it applies to near and distant objects equally. The motion may be in any direction, although the lateral component is usually the most prominent.

It is well known that nystagmus may produce an oscillating visual sensation in persons with conditions of many types and that the same phenomenon occurs in normal persons during the nystagmus of vestibular tests. The oscillation under consideration is of a different and more limited type, however; it is an oscillatory sensation associated specifically with certain phenomena of walking and fixation of gaze.

The mechanisms by which the oscillatory sensation is directly produced are easy to determine. Nystagmus is the most common; intention tremor of the head is rather frequent, and occasionally oscillopsia depends on *Zitterbewegungen*. Sometimes two or more factors are combined. In no instance has the symptom been observed unless at least one of these phenomena was present.

When nystagmus or tremor of the head is the cause, it is possible to observe the relation between the oscillation seen by the patient and the objective motion of the eyes or the head. It is only necessary for the examiner to walk backward, facing the patient, who is walking forward, and to have the patient hold one hand near his eyes, indicating with his fingers the rate and the direction of the oscillation. It is usually found that both correspond exactly with the objective movement of the eyes or the head.

Read at a meeting of the Philadelphia Neurological Society, April 26, 1935.

From the Neurological Institute of New York and the Department of Neurology, College of Physicians and Surgeons, Columbia University.

1. Brickner, Richard M.: Bull. Neurol. Inst. New York **5**:16, 1936.

But the fact that such movements as nystagmus and tremor of the head can produce oscillopsia does not explain the whole question; it merely moves the problem one step further back. Why is it that nystagmus or tremor of the head, which may be quiescent while the patient is at rest, is induced by walking? The tremor may well be looked on as of the intention variety; it is reasonable to suppose that the muscular tension involved in maintenance of the erect posture of the neck and head is thrown out of balance, with resultant tremor of the head when the foot strikes the ground in the taking of a step. Indeed, it can sometimes be observed that the tremor is decidedly accentuated each time the weight of the body is thrown on the stepping leg.

But can nystagmus also be thought of as an intention tremor? It might be hypothesized that the muscular effort required for holding the eyes fixed is increased when a step is taken and that this increased muscular tension is sufficient stimulus for the induction of intention tremor. This explanation receives some support from the case of one patient who had no oscillopsia but who experienced occasional diplopia, sometimes when at rest but usually on walking. A second patient had typical oscillopsia associated with diplopia on moving the head. In still another, oscillopsia and diplopia had previously occurred together on walking. The first of these patients showed, on examination, impairment of movement of the eyes in all directions. In the second there were coarse nystagmus with gaze in each direction as well as on fixation, weakness of several ocular muscles and tremor of the head on movement of the head. Because of the tremor, which was greatly exaggerated by walking, it was impossible to determine whether walking produced a change in the nystagmus or not. In the third patient, physical examination made at the time of the oscillopsia was incomplete, and the relevant data were not recorded.

It seems possible that the maintenance of the changed visual axes which these patients had acquired during the development of ocular paresis was disturbed during walking, perhaps by mere jarring, with resultant diplopia. If this is true, it seems possible that oscillopsia might also result from impairment of conjugate gaze, which might be accentuated by walking, just as nystagmus can be. In this connection it is interesting to recall the diplopia occasionally experienced by ordinary persons with ocular imbalance.

On the other hand, it appears possible that the increase in nystagmus is associated with some abnormality in the vestibulo-ocular pathways—an abnormality of such a nature that the static stimuli resulting from walking (step for step as the foot strikes the ground) are of greater intensity than normal, or at least affect the ocular nuclei to a greater degree than usual.

Caloric and rotation tests, which Dr. Page Northington performed in several cases, have not helped in clarifying the fundamental basis of the phenomenon. The vestibular reactions are still under investigation.

All that has been said in connection with walking may apply equally to fixation of gaze.

When nothing but *Zitterbewegungen* can be detected in a case of oscillopsia, the examiner is at a loss for means of observing what happens during walking, since that phenomenon can be observed only with the ophthalmoscope.

The symptom was manifested with considerable frequency in the series of sixty-two cases which has been alluded to. It occurred definitely in eight instances (12.9 per cent) and as diplopia without actual oscillopsia in another. However, data relevant to the matter were lacking in some of the earlier cases, in which the symptom was not sought but in which it might well have been present; so the incidence may have been even higher. The symptom has been seen five times in another group of patients (one of whom did not present typical multiple sclerosis).

The symptom may come on at any time during the course of the disease. In eight of the thirteen cases in which it has been seen, it developed within the first two years. In one (in which it was associated only with *Zitterbewegungen*) it was a first symptom.

Two typical descriptions of oscillopsia, taken from records of cases, follow:

J. H. F.: "I cannot read on either side while walking; I have to stop in order to see clearly. The words are blurred; they also wobble in circular fashion. This does not apply to other objects."

P. E.: "Objects seem to move up and down during walking." In this case the tremor of the head was vertical. When the patient looked sideways, following the examiner's finger with his eyes, the finger seemed to him to move sideways; at that time the nystagmus and the tremor were both lateral. Also, there was a certain amount of ocular dissociation on looking to the right—that is, the right eye did not come over as quickly as the left after it had passed the midline. When the patient stood still, if one pushed his head forward against his resistance and then released it, thus accentuating the tremor of the head, oscillopsia occurred and persisted until the accentuation of the tremor ceased. The oscilloptic movement was then vertical, and so was the tremor.

Oscillopsia is unquestionably frequent in cases of multiple sclerosis, but no claim is made that it is limited to this disease. As has already been noted, the first autopsy performed on a person in whom the symptom was observed revealed no sign of multiple sclerosis. Indeed, the nervous system was found to be normal. The lesion was presumably

labyrinthine, but unfortunately the labyrinths were not removed. In addition, the symptom was observed in the patient just mentioned, whose multiple sclerosis—if such it was—was atypical.

SUMMARY

A new symptom, oscillopsia, is described. It occurs commonly, but not exclusively, in patients with multiple sclerosis. It consists of an apparent oscillation of visualized objects. It occurs only on walking or on fixation of gaze. A variant of the symptom is diplopia elicited by walking; the diplopia may occur concomitantly with or independently of the oscillating sensation.

CALCIUM CONTENT OF THE BLOOD SERUM DURING AN EPILEPTIC CONVULSION

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AND

ALBERT W. PIGOTT, M.D.

SKILLMAN, N. J.

A review of the literature on the calcium content of the blood serum during an epileptic convulsion reveals no adequate series of cases with the values based on an accepted method. Determinations of the calcium content between seizures have been made by many workers. The values usually fall within normal limits. Bigwood,[1] Parhon and Ornstein,[2] and Di Renzo and Tomasino[3] reported values lower than normal, while others, namely, Patterson[4] and Hernandez del Valle,[5] reported levels above the upper limit of normal.

A study of the calcium content of the blood serum has been made on a series of fifty unselected, nonfasting patients with chronic epilepsy at the New Jersey State Village at Skillman. Blood was removed for determination of its calcium content during a major convulsive seizure and subsequently, from the same patients, between attacks.

METHOD

The specimens were taken between 1:45 and 2:30 p. m. and between 7:30 and 9:00 p. m. because the patients were at assembly and blood could be secured almost immediately if a seizure occurred. The patients ate at 7 a. m., 12 noon and

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From the New Jersey State Village for Epileptics.

Read before the Section on Convulsive Disorders at the Ninety-First Annual Meeting of the American Psychiatric Association, Washington, D. C., May 13, 1935.

1. Bigwood, E. J., cited by Lennox, W., and Allen, Margaret B.: Studies in Epilepsy: XI. The Calcium Content of the Blood and of the Spinal Fluid, Arch. Neurol. & Psychiat. **24**:1199 (Dec.) 1930.

2. Parhon, C. L., and Ornstein, J.: On the Calcium of the Blood and Spinal Cord in Epilepsy as Well as in Certain Psychoses, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:742, 1930.

3. Di Renzo, F., and Tomasino, A.: Research on the Behavior of Calcium and Potassium in the Blood of Epileptics in the Period Between Attacks and During Attacks, Rassegna di studi psichiat. **19**:503, 1930.

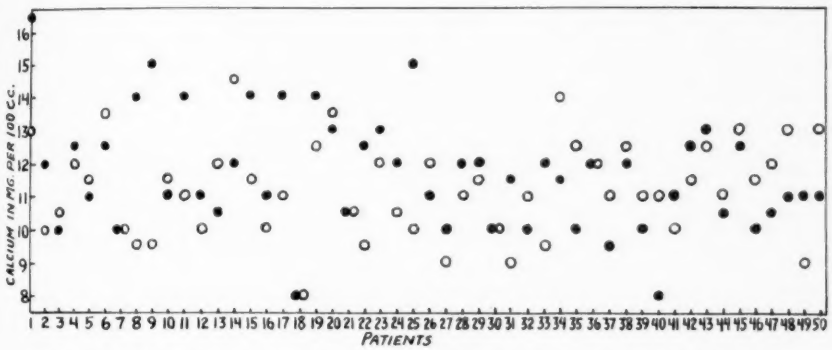
4. Patterson, H. A.: Some Observations on Blood Calcium Content in Epilepsy and the Convulsive States, Baltimore, Williams & Wilkins Company, 1931, vol. 7, pt. 1, p. 387.

5. Hernandez del Valle, P.: Calcium Content of Blood and Cerebrospinal Fluid: Potassium Content of Blood in Epileptics, Arch. cardiol. y hemat. **14**:150 (April) 1933.

6 p. m. The blood was taken by one of us (M. S.) during the late tonic and early and late clonic phases of the convulsion from a distended vein on the flexor surface of the forearm through an 18 gage needle into a 20 cc. sterile, dry calcium-free syringe; it was immediately placed in a dry calcium-free centrifuge tube and corked. The specimen was kept in a refrigerator at 45 F., and the serum calcium content was estimated within twenty-four hours by one of us (A. W. P.) using the method of Clark and Collip. A specimen was taken from each patient between seizures at approximately the same time of day as that taken during an attack. This blood was used as a control.

RESULTS

The total distribution of the serum calcium values during and between seizures is shown on the accompanying chart. The abscissas represent the patients and the ordinates the serum calcium in milligrams per hundred cubic centimeters of blood. The solid circles represent the values of specimens taken during an attack and the hollow circles the



A graph showing the distribution of calcium values during and between epileptic attacks. The solid circles represent the values of specimens taken during an attack and the hollow circles the values of those taken between attacks.

values of those taken between attacks. It can be seen that only three specimens had less than 9 mg., four had above 14 mg. and ninety-three had from 9 to 14 mg. per hundred cubic centimeters. Forty-five (90 per cent) of the specimens taken during a convulsion and forty-eight (96 per cent) of the control specimens had from 9 to 14 mg.

SUMMARY AND CONCLUSION

An estimation of the calcium content of the blood serum during a convulsion was made for fifty unselected, nonfasting institutionalized epileptic patients, and the value was compared with that of a control specimen taken between seizures. The type of epilepsy and associated factors, such as the race, the sex and the age of the patient, the length of time the disease had existed and the time of day and the presence

or absence of a convulsion when the specimen was taken, had no appreciable effect on the calcium level, which was from 9 to 14 mg. per hundred cubic centimeters in 93 per cent of the determinations, with an average for all specimens of 11.4 mg.

An adequate series of determinations made during a convulsion, with which we could compare our findings, was not available in the literature.

The determination of the calcium content of the blood serum during a seizure showed no appreciable difference from that made for the same patient between seizures. Our study shows that hypocalcemia is uncommon in patients with chronic epilepsy; a normal calcium content (from 9 to 11 mg. per hundred cubic centimeters) or hypercalcemia (a content of from 11 to 14 mg.) was the usual finding.

Technical and Occasional Notes

PARTIAL CEREBELLAR AGENESIS IN A DOG

R. C. Baker, Ph.D., and Grant O. Graves, M.D., Columbus, Ohio

In a review of the literature we were unable to find more than three papers which deal with agenesis of the cerebellum in animals. Russell in 1895 reported a case of diminution in size of the cerebellum in a dog [1] and a case of unilateral agenesis of the cerebellum in a cat.[2] Later, Cornwall [3] published a paper on a cat the cerebellum of which was reduced in all dimensions. It is thus evident that few cases dealing with this particular phase of agenesis have been reported. Likewise, only a small number in man have been described.[4]

REPORT OF CASE

History.—The dog, a mongrel, a cross between a Boston bull terrier and a Manchester terrier, was the only one of the litter that was abnormal. It was particularly noted that she did not walk at the usual time, but, as it was expected that she would later, she was kept in a kennel until 7 months old. At this time we obtained possession of the dog. Autopsy was performed at the end of the eighth month.

Observations at Autopsy.—The abdominal and thoracic viscera were normal in shape and position, and the musculature of the extremities was equally developed on both sides and showed no atrophy. The only external evidence of abnormality of a structural nature was right-sided harelip.

On exposure of the brain the dura was seen to be normal in appearance, as was the pia-arachnoid. Exploration of the posterior cranial fossa showed the tentorium to be well formed and normally related to the usual adjacent structures, the cerebellar cistern being filled with clear cerebrospinal fluid. Further inspection revealed the cerebellum to be markedly diminished in size; the vermis was absent, and the lateral hemispheres were exceedingly small, the left being the smaller. All the other parts of the brain appeared normal except the medulla, which externally revealed absence of the inferior olives.

Gross Appearance.—The cerebral hemispheres (fig. 1), on comparison with the configuration of the brain of the normal dog, showed no deviations. The dura covering the hemispheres was normal, the pia-arachnoid clear and smooth and the

1. Russell, J. S. R.: Defective Development of the Cerebellum in a Puppy, Brain **18**:523-530, 1895.

2. Russell, J. S. R.: Defective Development of the Central Nervous System in a Cat, Brain **18**:37-53, 1895.

3. Cornwall, L. H.: Cerebro-Cerebellar Agenesis in Its Relation to Cerebellar Function, Brain **50**:562-572, 1927.

4. Baker, R. C., and Graves, G. O.: Cerebellar Agenesis, Arch. Neurol. & Psychiat. **25**:548-555 (March) 1931.

blood supply typically disposed. Both the dorsal and the ventral surface displayed sulci and gyri that were normal as to both size and shape. The olfactory nerves were present and of the usual size.

The diencephalon and mesencephalon were likewise of normal size and shape, as were the optic, oculomotor and trochlear nerves.

The rhombencephalon was the only division of the brain which in gross appearance presented anomalies that are interpreted as being associated with the partial agenesis of the cerebellum. There were total absence of the vermis and marked agenesis of both cerebellar hemispheres. Figure 2 shows this agenesic condition.

The left cerebellar hemisphere was represented by a small nodule of cortical material divided into small folia by anteroposterior sulci. In figure 3 *A*, *B* and *C* are shown in diagrammatic form the dorsal, the posterior and the left lateral view, respectively, of this hemisphere.

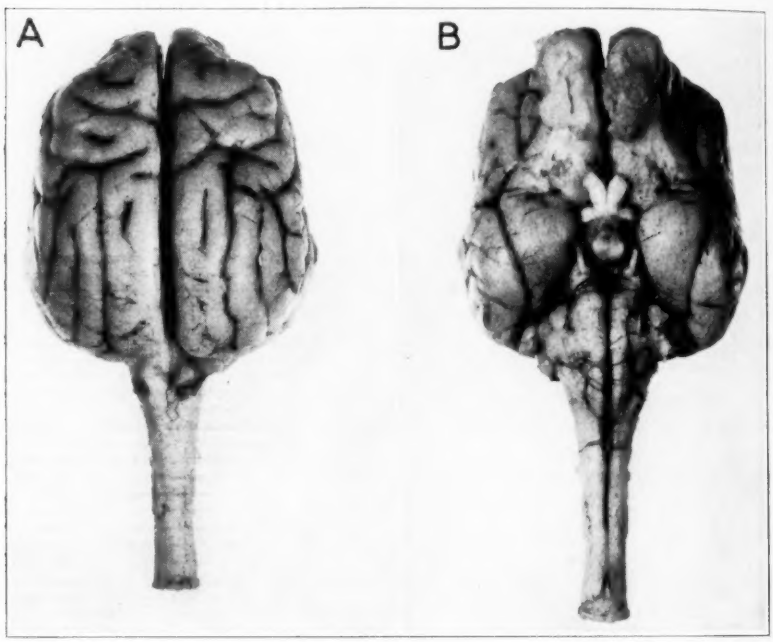


Fig. 1.—*A*, is a dorsal and *B*, a ventral view of the brain (actual size), showing normal configuration of the cerebral hemispheres. The pons is poorly defined from the medulla; the olivary eminence is invisible.

The vermis was absent. However, a narrow band of dark yellow material, approximately 2 mm. in width, was seen extending across the margins of the anterior velum of the fourth ventricle. A section of this band was removed in the midline. The parts lateral to this are shown in figure 2. Gross inspection of this structure did not show normal white and gray matter.

The right cerebellar hemisphere, owing to its more advanced development, requires a more detailed description. In this hemisphere there was a diminutive arrangement of the lateral lobes, closely duplicating the adult form. Although there was little grossly that represented the restiform body and the middle cere-

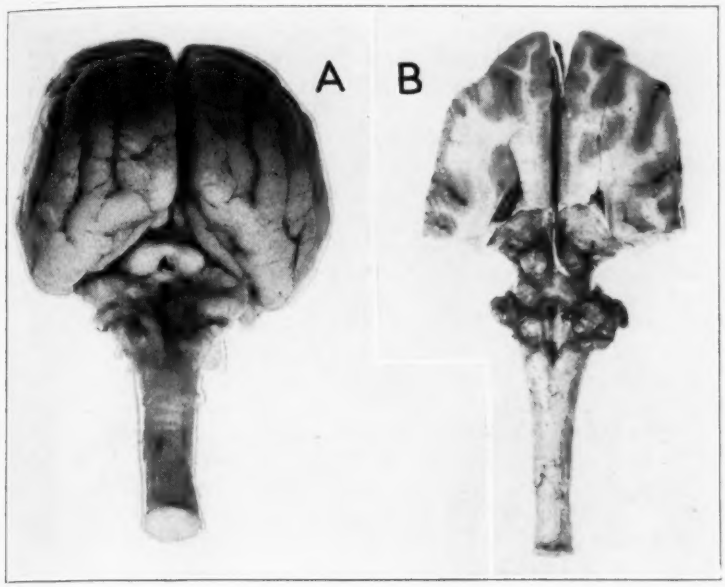


Fig. 2.— *A* and *B* are dorsal views (actual size) of the agenetic cerebellar hemispheres (*B* showing part of cerebral hemispheres cut away to expose the agenetic cerebellum and corpora quadrigemina). No vermis is present. The fourth ventricle is wide and has normal markings on the floor.

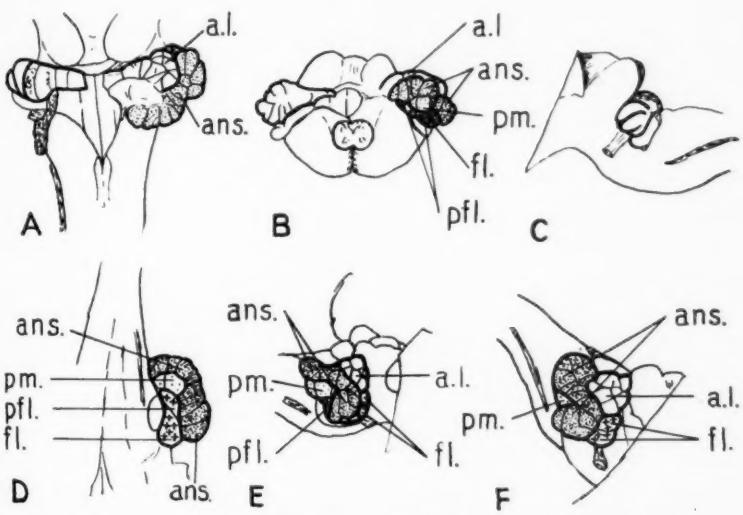


Fig. 3.—Diagrams of the agenetic cerebellar hemispheres, showing the component parts. *A* shows the dorsal view; *B*, the posterior view; *C*, the left lateral view; *D*, the ventral view; *E*, the right lateral view, and *F*, the right dorsal view. *a.l.* indicates the anterior lobe; *ans.*, the ansiform lobule; *fl.*, the flocculus; *pfl.*, the paraflocculus, and *pm.*, the paramedian lobule.

bellar peduncle, the brachium conjunctivum was clearly seen emerging from the hidden surfaces of the anterior and posterior lobes. The anterior lobe (fig. 3 *A, B, E* and *F, a.l.*) is represented in the figure in solid white. It was separated from the posterior lobe by a more prominent sulcus, which is represented by the heavy black line in figure 3 *A*. In the anterior part of the posterior lobe (represented by the dotted areas) we were able to distinguish the ansiform lobule (fig. 3 *A, B, D, E* and *F, ans.*) and the paramedian lobule (fig. 3 *B, D, E* and *F, pm.*). The posterior part of the posterior lobe (represented by the areas with crosses) may be subdivided into the paraflocculus (fig. 3 *B, D* and *E, pfl.*) and the flocculus (fig. 3 *B, D, E* and *F, fl.*). The base of the flocculus was firmly bound down to the medulla by the fibers from the vestibular area.

The right cerebellar hemisphere revealed more or less a coiled configuration, and its divisions, since they may not be clearly shown by a superficial examination of the photographs, will be briefly described: The anterior lobe extended laterally (fig. 3 *A, a.l.*) and ventrally (fig. 3 *E, a.l.*) from its attachment by white fibers at the border of the fourth ventricle and became confluent with the dorsal and posterior extensions of the ansiform lobule of the posterior lobe (fig. 3 *A* and *E, ans.*). At the posterior end of the ansiform lobule the posterior lobe curved abruptly ventrally and anteriorly and formed the paramedian lobule (fig. 3 *E, pm.*). This was continuous although demarcated by a fissure, and became confluent with the paraflocculus (fig. *E, pfl.*). The paraflocculus formed a loop which was convex venterally and extended into the flocculus (fig. 3 *E, fl.*). The flocculus thus lay anterior to the paraflocculus (fig. 3 *D, fl.*) and had, therefore, a much shorter fibrillar stalk attaching it to the dorsolateral wall of the medulla. This type of diminutive arrangement of the hemisphere closely resembles the adult form and is not uncommonly seen in partial agenesis that has developed beyond a certain stage. We recently described a similar arrangement of a partially agenesic cerebellum in man.[5]

The medulla presented some anomalies characteristic of cerebellar agenesis. The fourth ventricle was somewhat wider than normal, although this did not affect the surface markings, on its floor. On external examination the olives were not visible on either side. We have observed the same anomalies in a case in man.[6] The dividing line of the pons and medulla proper (as shown in figure 2 illustrating our report of this case) was not well defined. All the nerves were present and of the normal size and position.

Microscopic Appearance.—The microscopic sections were chosen to illustrate the condition of the chief nuclei and tracts concerned with cerebellar functions, namely, the roof, the olivary and pontile nuclei, the restiform body, the brachium pontis, the brachium conjunctivum and the vestibulocerebellar tracts. The absence of the vermis and the greatly reduced lateral lobes of the cerebellar hemispheres presented difficulties in identifying some tracts which are easily recognized in a normal brain.

In figure 4, which shows a section taken at the level of the commissural nucleus of Cajal (the vagal commissure of Papez) and at the middle of the decussation of the fillet, posterior to the middle of the olive, the difference in size of the left olive sending fibers to the larger right cerebellar hemisphere and the right olive sending fibers to the smaller left hemisphere is evident. The inferior olive consisted largely of the dorsal and ventral accessory olivary nuclei (*d.acc.ol., v.acc.ol.*), there being only a trace of the olivary sac as defined by

5. Footnote 4, case 1.
6. Footnote 4, case 2.

Papez.[7] On the left, the dorsal and ventral nuclei were joined and formed a curved mass with the hilus directed laterally. This condition did not exist on the opposite side. Only a trace of the olive was visible; this occupied a region just lateral to the emerging fibers of the glossopharyngeal nerve.

The dorsal and ventral spinocerebellar tracts appeared to be absent. At the level of the middle of the inferior olive the restiform bodies could be recognized; the one on the right was more pronounced, and microscopically its fibers were distinctly larger (fig. 5, *c.res.*). Caudal to this level the spinocerebellar tracts in a normal brain are mingled with the fibers of the spinal lemniscus and are not easily recognized. The relatively huge size of the trigeminal nucleus and the trigeminospinal tract (fig. 5, *trig. sp.*) might have concealed spinocerebellar fibers, but since the spinocerebellar fibers would have a ventrodorsal course and could be distinguished from the transversely cut trigeminospinal fibers it was assumed that the corpus restiforme was largely, if not exclusively, composed of olivo-

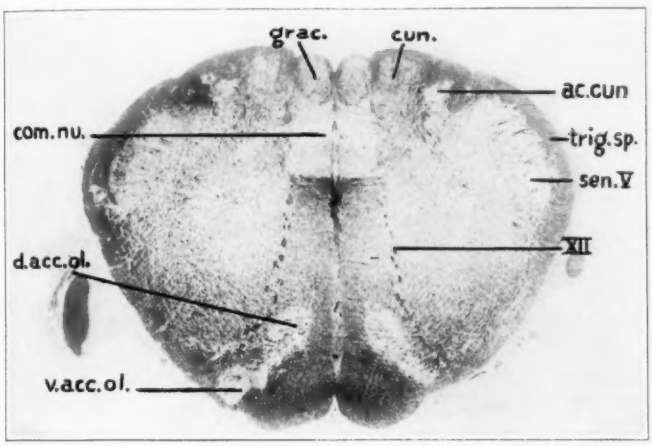


Fig. 4.—Photograph of a section taken at a level posterior to the middle of the inferior olive, showing the larger left nuclei. The dorsal and ventral accessory olivary nuclei are labeled *d.acc.ol.* and *v.acc.ol.* The hypoglossal nerve is indicated by the terminal nucleus of the trigeminal sensory fibers by *sen. V*, the trigeminospinal tract by *trig. sp.*, the accessory cuneate nucleus by *ac. cun.* and the nucleus gracilis by *grac.* The cuneate nuclei are labeled *cun.*, and the commissural nucleus of Cajal is indicated by *com. nu.* Weigert stain; × 7.

cerebellar and vestibulocerebellar fibers. The small size of the fibers in the corpus restiforme and the absence of the vermis in the cerebellum pointed to the same conclusion. The nucleus reticularis lateralis, along with fibers from that nucleus to the cerebellum, were absent, and although a well defined brachium conjunctivum and nucleus ruber were present, a rubrospinal tract could not be identified.

The roof of the rhombencephalon, while present and thickened, contained no normal nerve cells. The extreme caudal portion of the roof of the fourth ventricle was thin, and no choroid plexus was present, although it may have been

7. Papez, J. W.: Comparative Neurology, New York, Thomas Y. Crowell Company, 1929.

removed on detachment of a portion of the roof in examination of the floor of the ventricle. The rostral two thirds of the roof was thick, and its middle portion was separated into two areas by a nonvascular cavity. Corresponding to the same area in the normal brain as defined by Marburg,[8] the roof contained two commissures. A posterior commissure extended from the cerebellar hemispheres of each side in a rostral direction but did not extend completely across the roof of the fourth ventricle at its caudal portion. The anterior commissure was larger and appeared in the anterior medullary velum as far rostral as the decussation of the fourth nerve. The fibers forming this commissure apparently had their origin in the vestibular nuclei.

Figure 6 is a photograph of a section taken at the level of the rostral border of the superior olive (*ol. sup.*). It shows the cerebellum and brain stem in this region, particularly the agenetic character of the former. The three cerebellar peduncles appeared distinctly on the right side but were less well defined on the opposite side, where the brachium pontis entered the diminutive cerebellar hemisphere at a more caudal level. The mass of fibers (*br. pon.*) contained a large contingent of vestibulocerebellar fibers, which were traced to this region, where they entered the brachium pontis.

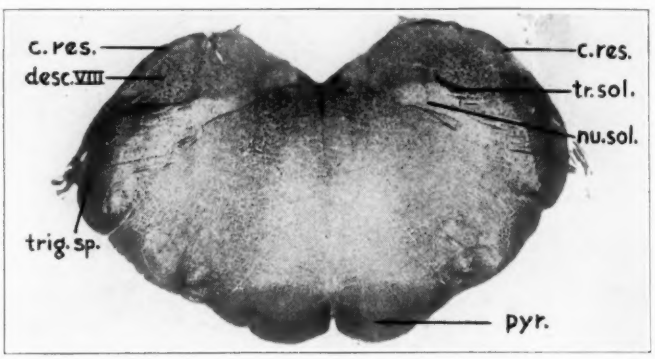


Fig. 5.—Photograph of a section taken through the middle of the inferior olive, showing the larger right restiform body (*c. res.*). The descending vestibular nucleus is labeled *desc. VIII*; the tractus solitarius, *tr. sol.*, and the nucleus solitarius, *nu. sol.* The pyramidal tract (*pyr.*) is of uniform size throughout the midbrain and medulla. Weigert stain; × 7.

The roof nuclei, consisting of a well defined group of cells showing no resemblance to these nuclei in either the cat or the dog, gave rise to the axons forming the brachium conjunctivum, which was decidedly more pronounced on the right side. This group of cells appeared to be caudal to the level shown in figure 6 and was located in the general position of the brachium conjunctivum and the corpus restiforme as shown in figure 6 (*br. conj., c.res.*). The divisions which constituted the nucleus fastigii, nucleus globosus, nucleus emboliformis and nucleus dentatus were not to be recognized.

The greatest reduction in tracts and nuclei concerned with cerebellar function occurred in the pontile nuclei and the brachium pontis. The brachium pontis arose

8. Marburg, Otto: Mikroskopisch-topographischer Atlas des menschlichen Zentralnervensystems, Leipzig, Franz Deuticke, 1910.

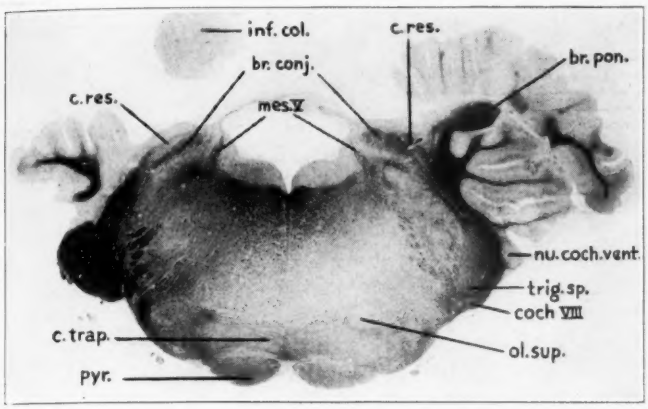


Fig. 6.—Photograph of a section taken at the level of the rostral border of the superior olive (*ol. sup.*) and the trapezoid body (*c. trap.*), showing the agenesic cerebellar hemispheres and their three peduncles—the brachium pontis (*br. pon.*), the brachium conjunctivum (*br. conj.*) and the corpus restiforme (*c. res.*). The cochlear nerve is labeled *coch. VIII*; the trigeminospinal nerve, *trig. sp.*; the ventral cochlear nucleus, *nu. coch. vent.*; the tract of the mesencephalic fibers of the fifth nerve, *mes. V*, and a pyramidal tract, *pyr.* Weigert stain; ×7.

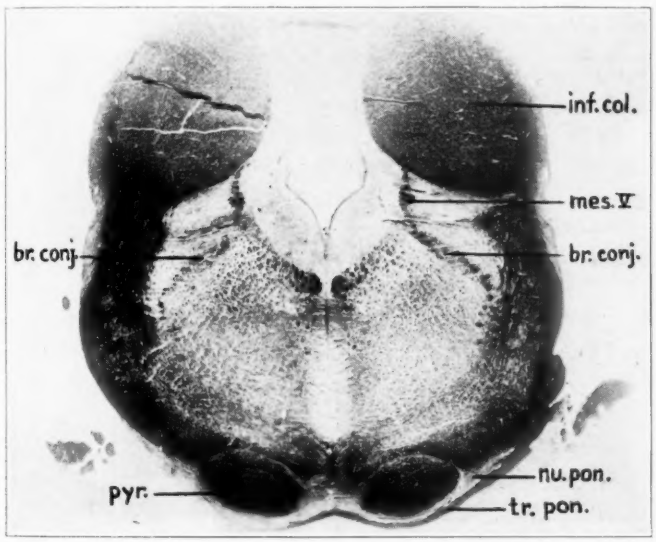


Fig. 7.—Photograph of a section taken at the level of the diminutive pontile nuclei (*nu. pon.*) and tracts (*tr. pon.*), cutting likewise the rostral end of the inferior colliculus (*inf. col.*). The mesencephalic fibers of the fifth nerve (*mes. V*) form a continuous band with the brachium conjunctivum (*br. conj.*) only on the right side. Weigert stain; ×7.

from a narrow strip of gray matter situated well rostral in the usual position of the pons (fig. 7, *nu. pon.*). Figure 7 is a photogrpah of a section taken near the rostral portion of the inferior colliculus. It shows the diminutive pontile nuclei and the fibers forming the brachium pontis. On the right side the brachium conjunctivum seemed to form a continuous band with the mesencephalic fibers of the fifth nerve, but on the left side these two tracts were not so intimately related (fig. 7, *mes. V., br. conj.*). The most caudal and ventral portions of the decussation of the brachium conjunctivum appeared in this section. It was difficult, however, to distinguish decussating fibers of the brachium conjunctivum from pontile fibers crossing at a more dorsal level.

The vestibulocerebellar fibers formed a well defined bundle entering the core of the cerebellum. These fibers were the largest entering the cerebellum. They usually enter the flocculus and the paraflocculus, but since the core of the cerebellum was dense they could not be definitely traced to these regions. The descending fibers from the cerebellum to the vestibular nuclei and other bulbar nuclei, including the vestibulospinal tract, could not be identified with certainty.

The pyramidal tract, owing to the reduction of the pontile nuclei, maintained an almost uniform size throughout the midbrain and bulb and was normal in other respects; the fasciculus longitudinalis medialis and the lemniscus medialis were normal. The accurate control of movements of the head and eyes, aside from that by the impulses of the visual and cervical nerves, probably is to be attributed to the normal vestibular mechanism.

All the bulbar nerves were normal and, owing to the reduction of tracts and nuclei concerned with the cerebellum, presented a striking picture of bulbar conformation.

The histologic structure of the lateral lobes, the flocculus and the paraflocculus was normal and showed no indications of degeneration. This condition pointed definitely to failure of development of the vermis and associated structures and not to degenerative processes the gross appearance of which may simulate a picture comparable to that of this agenetic cerebellum.

SUMMARY

Autopsy of the dog showed complete absence of the vermis and partial agenesis of both cerebellar hemispheres, which was more marked on the left side. Sections stained by the Weigert method showed the presence of small incoming and outgoing cerebellar tracts, tiny olivary nuclei and small pontile nuclei with resulting large spinal pyramidal tracts.

Case Reports

METASTATIC MELANOMA INVOLVING THE CENTRAL NERVOUS SYSTEM

HERMAN WORTIS, M.D., AND S. BERNARD WORTIS, M.D., NEW YORK

Melanomatous tumor of the skin or choroid is said to metastasize frequently to the central nervous system, but reports of few cases have been collected in which the pathologic invasion has been accurately studied. In reviewing the records at the Bellevue Hospital we found six cases of melanoma with metastases to the central nervous system. The characteristic life history of such a tumor has been described in previous reports by Fuchs,[1] Dawson,[2] Bramwell,[3] Grant,[4] Ewing,[5] Globus and Selinsky [6] and Bailey.[7] It should be emphasized that most of the cases have not been recognized until the postmortem examination, but it appears to us that there are several helpful criteria that should aid in the recognition of the tumor.

The clinical records and the associated pathologic changes in the cases at the Bellevue Hospital follow:

CASE 1.—C. M., a man aged 45, a Puerto Rican, was admitted to the hospital on Jan. 22, 1928, in a state of coma. His wife said that he had had a painful, bleeding black hairy mole over the right scapular region, which grew larger and was excised at another hospital nine months before and again three weeks before admission to the Bellevue Hospital. About six weeks before admission headache and vomiting developed. After the second operation the patient became progressively stuporous.

Read before the Section of Neurology and Psychiatry of the New York Academy of Medicine, Oct. 8, 1935.

From the Neurological Service, the Bellevue Hospital and the Department of Neurology, New York University College of Medicine.

1. Fuchs, E.: Textbook of Ophthalmology, ed. 6, Philadelphia, J. B. Lippincott Company, 1932, p. 474.

2. Dawson, J. W.: Edinburgh M. J. **32**:501, 1925.

3. Bramwell, B.: Atlas of Clinical Medicine, Edinburgh, T. & A. Constable, 1898, vol. 2, p. 47.

4. Grant, F. C.: Ann Surg. **84**:635, 1926.

5. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, p. 919.

6. Globus, J. H., and Selinsky, H.: Metastatic Tumors of the Brain: A Clinical Study of Twelve Cases with Necropsy, Arch. Neurol. & Psychiat. **17**:481 (April) 1927.

7. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 152 and 365.

Physical Examination.—The man was in a state of deep coma. The subcutaneous tissues all over the body contained numerous bluish-black rubbery nodules. Over the left scapular region was an infected wound, the site of excision of the primary tumor. Pupillary reactions were absent. Bilateral papilledema, stiffness of the neck and a bilateral Kernig sign were present. All deep reflexes were absent. The Babinski sign was not elicited. The liver was enlarged to 4 fingerbreadths below the costal margin, and there was also enlargement of the submaxillary lymph nodes.

The cerebrospinal fluid was under increased pressure and mixed with blood. Microscopic examination revealed large brownish-black pigmented cells (melanoma cells). The temperature was normal, and the pulse rate varied between 140 and 160. The urine was normal. A test for melanin was not made.

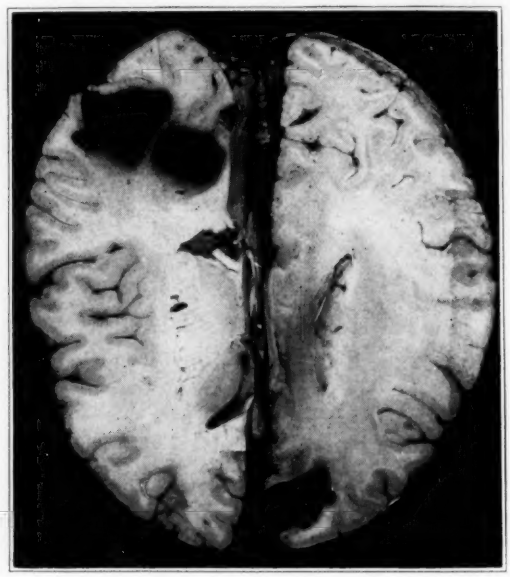


Fig. 1. (case 1).—Melanotic tumors in the left frontal and right occipital areas of the brain.

Course.—The patient died two days after admission, and autopsy showed disseminated melanosarcomatosis involving the skin, intercostal muscles, myocardium, lungs, liver, spleen, kidneys, adrenal glands, prostate, brain and meninges. There were multiple melanotic tumors of the brain involving the left frontal, left temporoparietal, left temporo-occipital and right calcarine areas.

Case 2.—K. K., a man aged 41, a Russian, was admitted to the hospital on Oct. 18, 1930, with the complaint of headache, pain in the stomach and vomiting after meals. In 1921 he had injured his right eye and lost sight in that eye. In 1926 he was told that he had a tumor in the right eye and was advised to have it enucleated; he refused until April 1929, when the eye was removed at another hospital. Four months prior to admission he began to have headache, pain in the epigastrium and vomiting.

Examination.—The left pupil was sluggish but reacted in accommodation. In the region of the right parotid gland there was a hard, freely movable mass with overlying brownish discolored skin. The right submaxillary lymph nodes were stony hard. The edge of the liver was 2 fingerbreadths below the right costal margin, and there was also moderate ascites. There were signs of fluid in the chest at the bases of both lungs.

Melanin was found in the urine on several occasions. The red blood cells numbered 3,200,000, with 65 per cent hemoglobin; the white blood cells numbered 8,500, with 78 per cent polymorphonuclears. The Wassermann reaction of the blood was negative.

Biopsy of a tumor in the neck showed it to be melanosarcoma.

Course.—The patient continued to lose weight and strength and became disoriented or confused and comatose before he died, on Oct. 23, 1930.

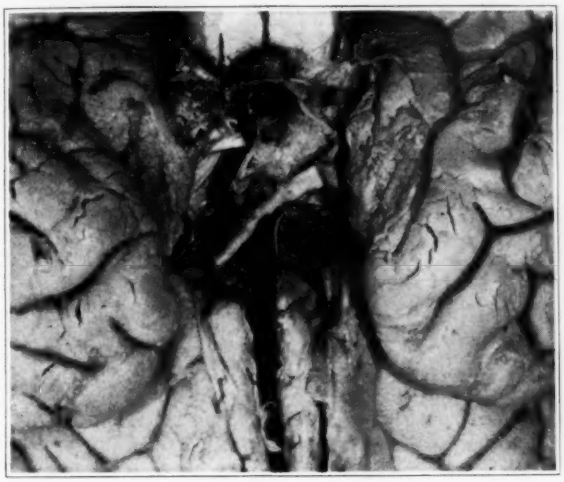


Fig. 2 (case 2).—Melanotic tumor in the region of the right optic nerve; extension metastasis from the right eye.

Autopsy.—There was generalized melanosarcomatosis, apparently primary in the orbit, with metastatic involvement of the meninges and sheaths of the right optic facial and auditory nerves, right frontal lobe of the brain, kidneys, liver, pancreas, skin and subcutaneous tissue, stomach, heart, bladder, lungs, pleura and mesentery, with generalized evidences of ascites.

CASE 3.—P. C., an American man, aged 60, was admitted to the hospital on Oct. 22, 1930, with the complaint of tumors of the neck, body and legs of two years' duration. Ten years before he noticed a small pigmented mole on the left side of the neck, which was removed by burning with acid. Two years before he entered the hospital the pigmented mole recurred and was excised after preliminary roentgen irradiation. Since, he had noticed small hard nodules all over the body. The urine became dark in color. One month before coming to the hospital he became dyspneic, and swelling of the ankles, anorexia and some diarrhea developed. He lost weight rapidly and had severe headache.

Physical Examination.—The patient was emaciated, with a dusky slate-colored complexion and multiple slate-colored tumors all over the skin and the scalp. There were pigmented areas (melanomas) of the right iris and left choroid. The liver was nodular and palpable 10 cm. below the right costal margin. The spleen was enlarged. There were conglomerate slate-colored nodes involving the right submaxillary region and both axillary regions. Several nodular masses were felt in the posterior rectal wall.

The urine showed considerable melanin pigment. The red blood cells numbered 3,890,000, with 71 per cent hemoglobin; the white blood cells numbered 10,200, with 75 per cent polymorphonuclears. Roentgenograms of the chest were normal. Roentgenograms of the gastro-intestinal tract revealed an irregular filling defect in the fundus of the stomach, which the roentgenologist believed was due to malignant infiltration. The blood chemistry was normal. Lumbar puncture was not performed.

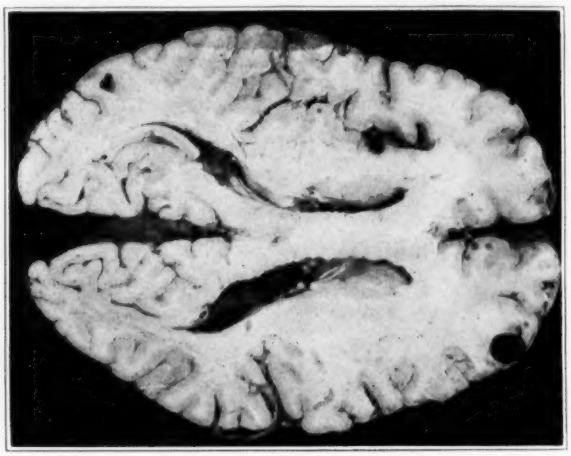


Fig. 3 (case 3).—Melanotic tumors in right frontal and left occipital regions.

Course.—The temperature and the pulse and respiratory rates remained normal throughout the patient's stay in the hospital. The headache continued to be severe. The patient became irrational and comatose before death, on Oct. 29, 1930, seven days after admission.

Autopsy.—There was generalized melanosarcomatosis, with metastatic tumors involving the heart, lungs, liver, spleen, kidneys, bladder, adrenal glands, entire gastro-intestinal tract, peritoneum, omentum, portal vein, skin, bones, brain, right eye (iris) and meninges. The brain was studded with melanotic tumors, of which the larger ones occupied the right frontal, left insular and left occipital regions.

Case 4.—G. W., an Austrian man, aged 40, was admitted to the hospital on Oct. 24, 1931, with the complaint of severe headache, loss of weight, pain in the posterior part of the right side of the chest and blood in the stools for one month. Ten years before he had first noticed a tumor of the right flank, which was removed four years ago (tumor not identified). Three weeks before the onset of symptoms, while he was being shaved by a barber, a small brownish wart on the

right cheek was accidentally cut. It bled profusely and subsequently began to turn black and enlarge.

Examination.—Multiple subcutaneous bluish tumors were present. The pupils were irregular and unequal (left larger than right) and did not react to light. The retinal vessels of both fundi were engorged, and in the left disk three small slate-colored tumors were observed. The cervical lymph nodes were enlarged, especially on the left side. The liver was enlarged to 3 fingerbreadths below the right costal margin and was nodular and tender. One of the nodules removed from the subcutaneous tissue of the right thigh proved to be melanosarcoma. The urine was tested twice for the presence of melanin, but none was found. The Wassermann reaction of the blood was 4 plus, which probably accounted for the pupillary changes. Roentgenograms of the pulmonary fields showed bronchiectasis, while those of the skull, long bones and pelvis were normal. Roentgenograms made after an enema of barium sulfate showed no evidences of an organic lesion

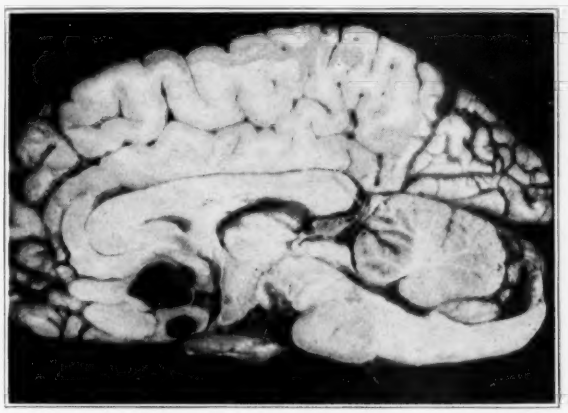


Fig. 4 (case 4).—Melanotic tumor invading the right subfrontal region.

of the colon. The red blood cells numbered 5,260,000, with 58 per cent hemoglobin; the white blood cells numbered 7,050, with 62 per cent polymorphonuclears.

Course.—The patient became progressively weaker; evidence of metastatic melanosarcomatosis became more apparent; the left eye protruded and became blind. He died on Nov. 30, 1931.

Autopsy.—There was generalized melanosarcomatosis involving the heart, aorta, lungs, liver, spleen, kidneys, skin, gastro-intestinal tract, lymphatics and brain. Melanotic tumors invaded the left frontal and occipital lobes and the right subfrontal and subcortical areas.

CASE 5.—E. H., a German woman aged 40, was admitted to the hospital on May 10, 1934, with the complaint of headache, pain in the lower part of the spine, radiating down the back of both thighs to the ankles, and numbness of the right hand along the outer three fingers for eight weeks. She had had (in 1932) a large flat brownish mole of the scalp just above the left ear, which bled profusely after a minor injury caused by combing her hair. After this incident the "mole" was removed by a physician, who identified it as melanosarcoma. One month later he removed some enlarged lymph nodes in the left submaxillary region, after which

high voltage roentgen therapy was given to the region of the neck. In March 1934 the pain in the lower part of the spine commenced. In the hospital the patient had jacksonian seizures on the right side, involving the face and arm, without loss of consciousness.

Physical Examination.—There was a nontender enlarged lymph node in the right submaxillary region. There was swelling of the left optic nerve head. The right palpebral fissure was wider than the left. There was weakness of the lower part of the right side of the face and of the right arm. Ataxy was shown in performing the finger-to-nose test on the right only when the eyes were closed. The deep reflexes were normal except for diminished ankle jerks. There was no Babinski sign. The patient could not recognize objects placed in her right hand. Sensibility to pinprick and to touch was diminished in the fingers of the right hand. Position sense was impaired in the thumb and index finger of the right hand.

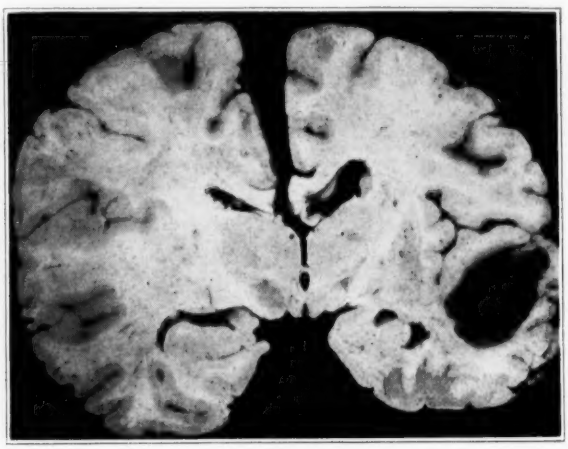


Fig. 5 (case 6).—Melanoma in the left temporal lobe.

Melanin was found in the urine and cerebrospinal fluid, the latter being xanthochromic. The red blood cells numbered 4,000,000, with 80 per cent hemoglobin; the white blood cells numbered 7,500, with a normal differential count. The Wassermann test of the blood and cerebrospinal fluid was negative. Roentgenograms of the skull and spine were normal.

Course.—The patient refused to remain in the hospital, but in view of the report on the biopsy of the tumors of the scalp and lymph nodes, the finding of melanin in the cerebrospinal fluid and the neurologic signs, the diagnosis of melanosarcoma metastatic to the central nervous system with a focus in the left frontoparietal cortex and diffusion throughout the subarachnoid spaces was made. A follow-up letter to this patient was not answered; her present status is unknown.

Case 6.—T. C., an American man aged 43, was admitted to the hospital on Jan. 27, 1935, with the complaint of headache, blurring of vision and vomiting for four months. The patient had been in a New York state prison for three and one-half years prior to admission, having been convicted for embezzlement of funds.

At the time of release from prison he is said to have been overtalkative, overactive, euphoric and disoriented. He became unreasonable and untidy in manners. At this time he was seen by Dr. E. D. Friedman, who referred him to the Bellevue Hospital.

Examination.—The pupils were unequal (left greater than right) and reacted in accommodation but not to light. In the left fundus, at from 4 to 8 o'clock, there was an inward displacement of the retina by a slate-colored tumor. The retinal vessels were congested, and the fundi both showed a moderate degree of papilledema. The patient was euphoric, overtalkative, garrulous and disoriented. The left biceps and ankle jerks were greater than the right. Both knee jerks were diminished, and the right ankle jerk was not obtained. There was no Babinski sign. Sensation was not impaired.

The liver was slightly enlarged, but not tender. There were a small lymph node in the left axilla and multiple painless subcutaneous tumors, varying in size from 1 by 1 to 4 by 4 cm., which were firmly adherent to the overlying skin but not attached to the deeper tissues. One large mass, 4 by 9 cm., deep

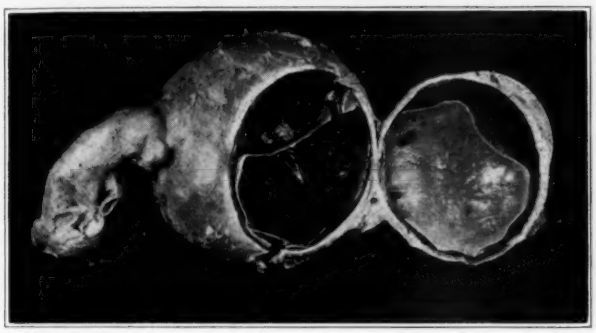


Fig. 6 (case 6).—Melanoma of the choroid invading the eye and displacing the retina before it.

in the left anterolateral region of the thigh appeared to be attached to the underlying muscle. The smaller tumors were distributed over the abdomen, back and gluteal regions.

The Wassermann reactions in the blood and cerebrospinal fluid were negative. The spinal fluid pressure was 650 mm. (water), and the fluid was slightly xanthochromic, with 11 lymphocytes, 112 mg. of protein, 679 mg. of chlorides and 25 mg. of sugar. The red blood cells numbered 3,700,000, with 82 per cent hemoglobin; the white blood cells numbered 10,600, with 60 per cent polymorphonuclears and a normal differential count. The blood chemistry and the urine were normal. The urine was tested for melanin, but none was found. Roentgenograms of the skull, chest and long bones were normal. Biopsy of a tumor of the skin, made on Feb. 8, 1935, showed melanosarcoma.

Course.—During the next two weeks the tumor in the left eye increased rapidly in size, and the patient became totally blind in that eye. He grew progressively more drowsy, then became comatose, and died on February 19, twenty-two days after admission.

Autopsy.—There were multiple brownish pigmented tumor nodules in the brain, subcutaneous tissues, lungs, myocardium, liver, kidneys, omentum, thyroid gland and fascia surrounding the left adrenal gland. The tumor of the left eye was a large melanosarcoma which invaded the entire posterior chamber and was probably the primary growth. The metastatic tumors in the brain were in the posterior third of the right superior frontal gyrus, the right cerebellar hemisphere and the left temporal lobe. The third and the left lateral ventricle were dilated.

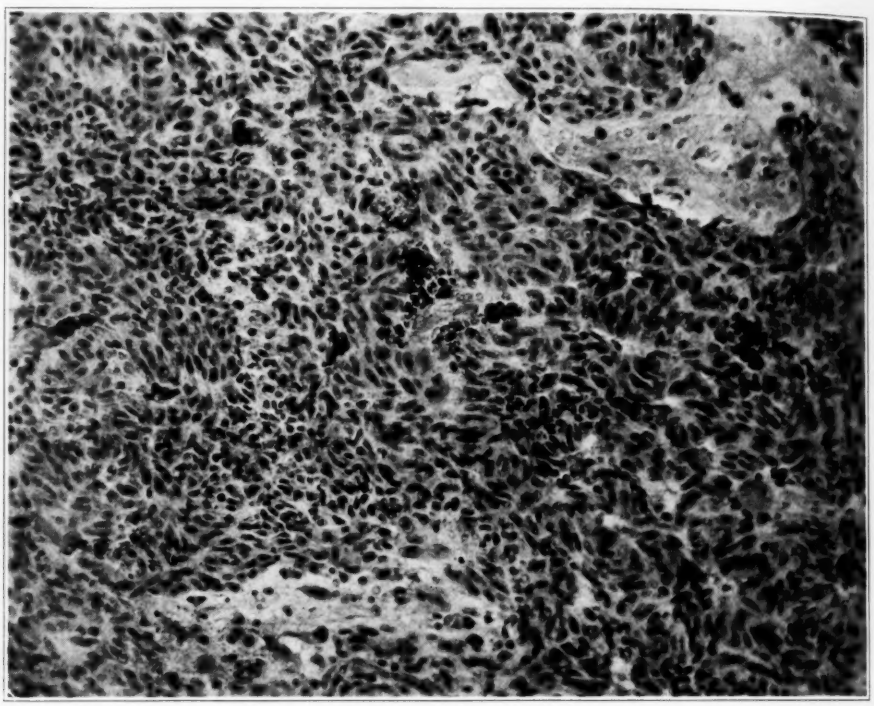


Fig. 7 (case 6).—Photomicrograph of melanotic tumor of the brain showing collections of deeply pigmented melanoma cells.

COMMENT

The commonest malignant tumor of the choroid is melanosarcoma, and one third of all melanomas originate here. Knight [8] has reported such cases. Pigmented nevi and melanoma also occur in the iris, the conjunctiva and the sheaths of the optic nerves. Fuchs [1] differentiated four clinicopathologic stages in the course of such a tumor. The first stage consists of detachment of the retina by the melanotic tumor; this stage is associated with impairment of vision, a defect in the visual field

8. Knight, M. S.: Melanotic Neoplasms of the Eye, J. A. M. A. **83**:1062 (Oct. 4) 1924.

or complete blindness of the eye. The second stage consists of a period of increased intra-ocular tension associated with pain, the condition of the eye resembling that observed in inflammatory glaucoma. Melanosarcoma may be differentiated from inflammatory glaucoma, with which it is often confused, by the fact that persons with melanosarcoma always become blind before the onset of pain in the eye, whereas those suffering from ordinary glaucoma become blind after having much pain in the eye. The third stage is reached when the tumor breaks through the eye, and the pain ceases. In the final stage, generalized metastases become evident and invade the skin, liver, central nervous system and other viscera, thereby confusing the picture so that the primary focus is often overlooked. Cure can be obtained in 60 to 80 per cent of such cases by enucleation of the eye in the first stage of the disease. Dawson has commented on the long latent period between the appearance of intra-ocular melanoma and evidences of metastatic invasion of the body. The metastases may invade all the organs of the body, but the liver is the commonest site. Invasion of the liver results in melanuria.

Melanoma may also arise in the skin, rectum, meninges and other organs according to reports by Foot and Zeek,[9] Becker,[10] Farnell and Globus,[11] Golden, Masson and Ewing.[12] Less than twelve authentic cases of primary melanoblastoma of the meninges have been described. Bailey [7] referred to these in his book on intracranial tumors, and we shall not discuss this group further. Nevi of the skin (i. e., pigmented moles), the source of cutaneous melanoma, appear chiefly on the face, neck, back and soles. These areas are especially subject to trauma which may appear to be the cause of malignant degeneration. Rapid growth, increased vascularity or pigmentation and superficial ulceration or pain are the evidences of malignancy in a melanoma. At this stage wide excision should be carried out. Improper surgical treatment or reliance on natural cure results in rapid and fatal dissemination of the tumor.

There is dispute concerning the origin of melanoma. Golden, Masson and Ewing [12] expressed the belief that the tumor arises from the tactile corpuscles of Meissner and is therefore of nervous origin. The fact that it has been observed growing along the course of a peripheral nerve is noted as confirmatory evidence. Others believe that the tumor is of dermal origin. Ewing [5] stated that the "duration of the generalized disease is about three years, but intervals from ten to twenty-four years have been known to lapse between the time of excision of the primary tumor and evidences of secondary lesions. Only rarely does the disease run an acute course of a few weeks."

Grant [4] studied the cases of melanosarcoma at the Peter Bent Brigham Hospital for the period from 1914 to 1926. The diagnosis was verified in three cases and not verified in four. He found that the period elapsing

9. Foot, N. C., and Zeek, P.: Am. J. Path. **7**:605, 1931.

10. Becker, S. W.: Melanin Pigmentation: A Systematic Study of the Pigment of the Human Skin and Upper Mucous Membranes, with Special Consideration of Pigmented Dendritic Cells, Arch. Dermat. & Syph. **16**:259 (Sept.) 1927.

11. Farnell, F. J., and Globus, J. H.: Primary Melanoblastosis of the Leptomeninges and Brain, Arch. Neurol. & Psychiat. **25**:803 (April) 1931.

12. Golden, Masson and Ewing, cited by Bailey.[7]

between malignant changes in the original focus and death of the patient averaged fifty-nine months; the period between the onset of intracranial symptoms and death averaged seven months.

We wish to emphasize that in studying our group of six cases the following facts were noted: The patients were all in the age group of from 40 to 60 years. In five the patients had subcutaneous tumors and palpable enlargement of the liver; four had frank papilledema or retinal congestion and melanotic tumors of the eye and five had severe headache. Of the three cases in which the spinal fluid was studied the fluid was xanthochromic in two and bloody in one. Melanin pigment was found in one specimen of spinal fluid and melanoma cells in another. Only one patient had mental changes preceding other evident signs of focal involvement of the brain. Careful study of the clinical records shows that the time elapsing between irritation of the original melanotic focus in the skin and the onset of cerebral symptoms varied three weeks to ten years. The time elapsing between the onset of cerebral symptoms and death was much shorter, being from seven days to four months. The patients showed evidences of increased intracranial pressure (viz., headache, vomiting and dizziness) out of all proportion to the objective neurologic signs. The lesions are disseminated in the brain and produce symptoms simulating meningo-encephalitis.

Whenever bloody or xanthochromic spinal fluid is found in a patient who has melanomatous tumors of the skin the spinal fluid should be examined for the presence of melanin pigment or melanoma cells.[13]

Radical surgical treatment to remove the primary focus, whether it is a choroidal melanosarcoma or an irritated pigmented mole, should be accomplished at the earliest possible time.

DISCUSSION

DR. FOSTER KENNEDY: There is little to add, I think, to this presentation. It is a succinct and clear account of a condition which, if one thinks of it, is not particularly difficult to diagnose. "If one thinks of it" is often the very kernel of diagnosis, and it is important that one should see the patients in order that one think of melanosis as a possible explanation for rather peculiar phenomena—phenomena which might be difficult to diagnose otherwise.

There are three points in the paper that call for a little comment. First, the authors said that in certain cases twenty years elapsed from the time of primary excision to the time of metastasis, but were there any cases in which primary excision occurred and metastases never occurred? I do not know. I do not know whether removal of a melanoma early enough can prohibit the production of metastases. Second, I thought that the statement regarding the differential diagnosis of glaucoma versus melanoma of the choroid was exceedingly important, namely, that in cases of melanoma blindness came first and in cases of glaucoma pain came first—an easy and a natural situation to remember, but a concatenation of events which it is well to call to mind.

I have no constructive comment to make on the odd fact that all these tumors occurred in persons between the ages of 40 and 60. That, of course, is the period of high vitality of tumors. One does not often see tumor of the brain in persons over 60, but why should one not see melanoma in persons over 60?

13. Todd, I. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, ed. 6, Philadelphia, W. B. Saunders Company, 1927, p. 163.

In the average person pigmentation does not become disturbed or senile dark plaques of melanoid material do not become fixed in the skin of the face and on the backs of the hands until the age of 65. One knows the old hand by its numerous black freckles. Why does melanoma occur at a time when the apparatus of pigmentation has not as yet become sufficiently deteriorated to be apparent?

I think that these presentations have been concise, short and illuminating.

DR. S. BERNARD WORTIS: There are many cases of melanoma of the skin in which if the growth is properly removed metastasis does not occur. Most surgeons, I think, are aware of the fact that if such a tumor is not widely excised it does metastasize, and, generally speaking, proper treatment is usually accorded a melanoma. It is only in the rare case, such as those in which the patient uses acids in self-treatment or in which trauma has occurred before the surgeon can make proper excision that metastasis occurs. Melanoma is fatal in a short time once it starts disseminating, and this probably accounts for the fact that one does not see many cases in persons over 60.

It should be possible to diagnose melanoma early. It is important to note that in a large institution, like the Bellevue Hospital, where patients admitted for general surgical, medical and neurologic conditions are numerous, we found only six such cases, and from our reading of the literature I believe this is the largest group of cases of metastatic melanoma of the central nervous system to be reported. Such cases have been reported individually. I am interested in Dr. Kennedy's comments on the question of metastasis in relation to pigmentation of the skin and body. We have no explanation for this phenomenon and hope that the persons who are studying the biology and chemistry of cancer will be able to answer his query.

Obituaries

ALBERT M. BARRETT, M.D.
1871–1936

In May 1895 there came to the Kankakee Hospital for the Insane at Kankakee, Ill., a recent graduate of the Iowa State Medical School who had been chosen as pathologist of the Iowa State Hospital at Independence, Iowa, under Dr. Gershom Hill. This was Albert M. Barrett, a minister's son, who was eager to devote himself to the technic of the study of the brains of the insane—a happy, well balanced and well focused inquirer, as I remember him, thoroughly unsophisticated and unbiased, sensibly and practically interested in doing justice to the task and opportunity of studying the brain. There was nothing of an ulterior yearning or an immediate desire to determine "the" pathologic basis of insanity, generally mentioned as "not yet" available; the aim was sound and direct: that of acquiring the technic of studying the brain at autopsy. Such at least is my memory of this, my first pupil, a thoroughly unspoiled inquirer in one of the first laboratories exclusively devoted to an autopsy service, at the time when the interests of psychiatric research were focused on the study of the brain, as shown in the few publications of that period (1893-1896). Barrett again took up his work in Iowa but again was granted a leave of absence to join a group formed at what was then still called the Worcester Lunatic Hospital at Worcester, Mass., under Hosea M. Quinby, this time for a year's service on the junior staff, assembled to do justice to the whole of the hospital "routine," primarily in clinical work, but also to share the autopsy work, as my position with the hospital was still called that of the pathologist. Barrett's primary interest was in the pursuit of histologic technic, such as the trying out of Ford Robertson's neuroglia stain, while I should have liked him to devote himself whole-heartedly to obtaining a telling history of the newly admitted patient and of the rank and file of patients, some of whom might also come to autopsy. The year passed quickly, disturbed by a three months' absence on my part necessitated by the aftermath from a tubercle encountered at autopsy. This absence resulted in a closer connection of Barrett with the senior intern, Allen R. Diefendorf, who on his own initiative was starting his abstract and adaptation of Kraepelin's "Psychiatrie" and at the same time the preparation of a valuable study of serial sections of the brain with complete isolation of the optic system in one hemisphere. Barrett again returned to Iowa, still strongly oriented in the direction of pathologic anatomy. The next

step was the acceptance of a post at the Danvers State Hospital at Danvers, Mass., to which Dr. Charles W. Page called Barrett when the veteran pathologist, W. L. Worcester, succumbed to an infection contracted while performing an autopsy. Dr. Page had engaged Dr. Diefendorf as pathologist and leader of the staff during his year of superintendency at the Middletown State Hospital at Middletown, Conn., and had brought back to the Danvers State Hospital his interest

Albert M. Barrett.

1871–1936

in the methods of study initiated at the Worcester Lunatic Hospital, which were no longer exclusively devoted to autopsy observations. The Danvers State Hospital became the main interest of Councilman's pupil, E. E. Southard, and Barrett's connection with Southard, and for a time with Nissl and Alzheimer in Heidelberg, gave origin to a new trend of developments. In the meantime, Dr. Herdman's untiring efforts had brought about the building of the first university hospital for

psychiatry at Ann Arbor, Mich., and as neither August Hoch nor I was any longer available to take its direction as originally planned, the choice fell naturally on A. M. Barrett, who for thirty years was to be the leader in psychiatry west of the Alleghenies. Although still the outstanding "organically" interested psychiatrist, Barrett was thus obliged to devote himself to clinical work and teaching, much more so and earlier than Southard. He established an independent, well balanced trend in contact with the state hospitals of Michigan and became the head of the department of psychiatry in one of the best medical schools of the time.

For some time Dr. Barrett's publications concerned structural involvements, such as the problem of pernicious anemia and aphasia, but his teaching inevitably drew him also beyond kraepelinian nosology into the domain of the personality functions themselves. During the World War Ann Arbor became one of the training centers in psychiatry. Several of Barrett's pupils became leaders in court work and student guidance. Dr. Barrett himself and his immediate staff did outstanding work in the field of heredity and personality types, since the support of the laboratory had been reduced, and at the time of the abrupt closure of his career Dr. Barrett was engaged in a scrutiny of the unusually well studied schizophrenic material of the Psychopathic Hospital from the opening to the present time. During the last few years, true to his first bent, he again developed the histologic laboratory and its work, with the help of support from the foundations.

It is regrettable that the broad and sound clinical teaching of this active and very human representative of American psychiatry did not receive a systematic expression in a comprehensive and inclusive book form. At the time of his death Dr. Barrett was president of the American Neurological Association and was preparing the Salmon Lectures for 1937. He had been president of the American Psychiatric Association (1921-1922). In keeping with his nonostentatious nature and devotion to his immediate task as teacher and director of his department and the relations to the state hospital system, he taught more by example than in any dogmatic manner. Similarly, his personal and familial life was one of gentle friendships and warmth. His wife, to whom he was devoted, died after a protracted illness in 1930. Their only son at that time was just beginning to grow into his professional training and career in law which helped fill the gap with broadening and vital interests.

Dr. Barrett had been warned of the danger of vascular disease a few years before his death, but the warning did not lead to any modification of the natural and quiet pace of his steady activity. A cardiac distur-

bance occurred a few days before the final attack, which unexpectedly deprived the many friends and co-workers of a most beloved and most highly esteemed personality, in the midst of what might have been the culminating period of a well spent life.

Dr. Barrett's career constitutes an important chapter in American psychiatry—that of the development of the first full-fledged university clinic in psychiatry, state supported and in the service of a state university.

Abstracts from Current Literature

Physiology and Biochemistry

THE STATE OF CALCIUM IN THE FLUIDS OF THE BODY: I. THE CONDITIONS AFFECTING THE IONIZATION OF CALCIUM. FRANKLIN C. MCLEAN and A. BAIRD HASTINGS, J. Biol. Chem. **108**:285 (Jan.) 1935.

This paper, which deals with the factors concerned in the ionization of calcium in body fluids, is of fundamental importance in any interpretation of the relationship between the calcium content of blood serum and that of cerebrospinal fluid, ascitic fluid, pleural fluid and edema fluid. The authors have introduced a biologic method for direct estimation of calcium ion concentrations by the use of the isolated heart of the frog as an indicator.

They have made a number of observations on human cerebrospinal fluid and find that the ionization of calcium present corresponds closely to that in an artificially prepared solution of similar composition. There is no reason to postulate a bound but diffusible form of calcium in amounts larger than can be accounted for on the basis of the small amount of citrate in such fluids. They conclude that the ionization of calcium in the fluids of the body is determined chiefly by the protein content of the fluids and that the relationship between calcium and protein can, as a first approximation, be described by a simple mass law equation, yielding the ionization constant of calcium proteinate. From the standpoint of the ionization of calcium in protein-containing fluids, therefore, these fluids may be most simply thought of as solutions of calcium proteinate, which ionizes as a weak electrolyte into calcium and protein ions, with a residue of the unionized compound. With the total calcium and total protein content known, the concentration of calcium ions may be readily calculated.

This statement, presented as a first approximation, is an oversimplification of the conditions which actually exist in the fluids of the body. Other variables, including p_H, temperature, albumin-globulin ratio, magnesium and citrate, are known to influence the ionization of calcium in these fluids, but the individual and combined effects of these variables are small. They are of slight practical importance as compared with the calcium-protein relationship. IRVINE, Boston.

DEUTERIUM AS AN INDICATOR IN THE STUDY OF INTERMEDIARY METABOLISM. R. SCHOENHEIMER and D. RITTENBERG, J. Biol. Chem. **111**:163, 1935.

Schoenheimer and Rittenberg have studied the intermediary metabolism of fatty acids and cholesterol by introducing deuterium into them. It is of great importance for physicians to realize that substances such as sterols, which are present in large amounts in the brain, have an active intermediary metabolism. They are both synthesized and degraded in the body and possibly also in the central nervous system. Their close relationship with hormones, bile acids, cardiac glucosides and carcinogenic substances emphasizes again their vital importance to cells, and not least to those of the nervous system. PAGE, New York.

ELECTRIC IMPEDANCE AND PHASE ANGLE OF MUSCLE IN RIGOR. EMIL BOZLER and KENNETH S. COLE, J. Cell. & Comp. Physiol. **6**:229 (June 20) 1935.

A theory of the complex impedance of muscle has been outlined from measurements of the resistance and capacity over a wide frequency range. The sartorius muscle of the frog was found to be electrically equivalent to a network of resistances and to a single variable impedance element of the polarization type. This

element has a constant phase angle and an absolute value which is an inverse power function of the frequency. In experiments in which rigor was produced in muscle by allowing it to stand in iodo-acetic acid, the phase angle of the element and the infinite frequency resistance of the muscle remained unchanged when the muscle went from the relaxed to the contracted state, while the zero frequency resistance and the absolute value of the polarization impedance increased. From other experiments it was concluded that the internal conductivity and the volume concentration of the fibers are unchanged when they are measured in an iso-osmotic solution of sugar to which Ringer's solution is added and that the specific internal resistance of the fiber is about three times that found for fiber when it is measured in Ringer's solution alone.

CHORNYAK, Philadelphia.

TEMPERATURE OPTIMA IN THE FEEDING MECHANISM OF THE OYSTER, OSTREA GIGAS. A. E. HOPKINS, J. Exper. Zoöl. **71**:195 (Aug. 5) 1935.

Lamellibranchs pump water by means of paired, ciliated gills which filter out food particles and convey them to the mouth. The relative rate of flow thus produced was studied in the Japanese oyster (Ostrea gigas) from Puget Sound. The optimum temperature for the pumping of water by the gills was found to be about from 27 to 28 C., although at 20 C. the adductor muscle is most relaxed, so that the valves are widest open and interfere least with the flow of water. By experiments with specimens so prepared that the adductor muscle and mantle could not influence the rate of flow, it was shown that between 20 and from 27 to 28 C. the adductor muscle, controlling the shell and the border of the mantle, acts as a brake on the activity of the gills. Frequent displacements of the curve of activity of the gills occurred at different temperatures, most commonly at about 25 C. When plotted as logarithm of rate against reciprocal of the absolute temperature the values become resolved into curves consisting of rectilinear segments.

WYMAN, Boston.

THE PHYSIOLOGY OF DEEP-SEA DIVING. WILLIAM A. R. THOMPSON, Brit. M. J. **2**:208 (Aug. 3) 1935.

Poisoning due either to carbon dioxide or to oxygen and compressed air illness (caisson disease) are difficulties which still confront the deep sea diver. In each of these conditions such symptoms as loss of consciousness and convulsions indicate disturbances at the neurologic level. One of the problems which confronted the 1930 Admiralty Committee was the occurrence in divers of a sensation variously described as dizziness, faintness or partial loss of consciousness. These sensations occurred at depths beyond 200 feet. One of the most disconcerting features was that the diver continued to answer signals and even speak on the telephone, yet when he reached the submerged decompression chamber he could recall nothing of what happened in deep water. Illumination was established to prevent incoordination between the eyes and the semicircular canals, for at this level there is complete darkness. The use of a 3,000 candle-power lamp improved matters, but a few cases still occurred. The fact that some men were more prone to be affected than others suggested that the condition was more psychologic than physical, a speculation which was supported by the evidence that certain divers showed a steady improvement as the diving trials proceeded.

Some of the affected divers were examined by Prof. Millais Culpin, who decided that during these periods of semiconsciousness they were actually in a state of fugue. At the interview the so-called periods of semiconsciousness were reconstructed by the divers themselves, which suggested that in actual fact there was no loss of consciousness and that the state was a form of panic with suppression of the memory of events during this period. As a result of these findings the committee recommended that any tendencies to fear be treated with

suspicion and any sign of claustrophobia be sufficient to debar a man from deep diving. They state that "the type of man likely to be suitable for deep sea diving is the strongly built athletic type of even temperament." Two successive sets of diving trials have confirmed the value of these recommendations. Their adoption has been followed by a disappearance of symptoms.

BECK, Buffalo.

DISCHARGE FREQUENCIES IN THE CEREBRAL AND CEREBELLAR CORTEX. E. D. ADRIAN, J. Physiol. **83**:32 P (Feb. 9) 1935.

In an anesthetized cat or rabbit the spontaneous electrical activity of the cerebral cortex shows repeated groups of sinusoidal waves at frequencies ranging from 35 to 50 per second. Adrian and Matthews (1934) found that injury to the cortex gave a more regular discharge of similar waves, starting as a rule at from 90 to 60 per second and declining to from 40 to 35 per second, after which all trace of regularity is lost. Occasionally, with severe injury the rapid oscillations give place to a series of large waves, which continue to much lower frequencies (5 per second or less). Adrian and Matthews concluded that all these waves were due to synchronous discharges in groups of cortical neurons, that the frequency in these neurons seldom exceeds 100 per second and that from 50 to 35 per second is the characteristic rate for excitation of moderate intensity.

An entirely different picture is found in records of the potential changes in the exposed cerebellar cortex (vermis or lateral lobes) under anesthesia or in the decerebrate preparation. There is persistent spontaneous activity consisting of groups of sinusoidal waves at frequencies ranging from 250 to 150 per second, and there is no sign of the slower type of oscillation found in the cerebral cortex. In deep chloroform anesthesia the cerebellar waves often become exceedingly regular, but the rate is still 150 per second.

Electrical stimulation of the cerebral and cerebellar cortex reveals the same differences in the frequency of discharge. In the cerebrum stimulation with repeated induction shocks for a few seconds gives a discharge resembling that produced by severe injury. The initial stages are obscured by the stimulus artefact, but the frequency soon falls to a plateau at from 40 to 50 per second, and ultimately the discharge changes progressively into a series of large waves, which may attain very low frequencies. These resemble the waves due to convulsant drugs, and it can be shown that they spread widely over the cortex.

In the cerebellum electrical stimulation produces a regular series of waves (injury does not), but the whole frequency range is much higher. As in the cerebrum the initial frequency is still uncertain, but in the later stages of the discharge the waves occur at from 250 to 150 per second and cease when the frequency has fallen to 150 per second. Here, too, the waves spread some distance from the stimulated point and are evidently due to a number of neurons pulsating in phase.

The fact that the normal activity of the cerebellar neurons occurs at such high rates suggests that the cerebellum may perhaps exert an inhibitory influence of the Wedensky type on some of the structures innervated by it.

ALPERS, Philadelphia.

A FLEXOR RIGIDITY PREPARATION. R. J. S. MCDOWELL, J. Physiol. **83**:36P (Feb. 9) 1935.

Although it is well known that a spinal animal exhibits flexor rigidity, the production of spinal shock when the spinal cord is cut prevents convenient demonstrations of this phenomenon. If, however, the carotid arteries are tied and decerebration is performed, the animal being allowed to become rigid, and thereafter a clamp is applied to the vertebral arteries, the extensor rigidity is converted into a flexor rigidity. Sometimes this occurs with almost dramatic suddenness, the extended limbs being seen to flex, but more commonly the onset is slower

and is marked in fifteen to twenty minutes. A few animals continue to breathe and do not become spinal, the variation no doubt depending on the degree of anastomosis existing between other cerebral arteries and the arteries of the trunk, as described by Leonard Hill (1896).

ALPERS, Philadelphia.

ACTION OF ACETYLCHOLINE ON THE "SLEEP CENTRE." B. B. DIKSHIT, J. Physiol. **83**:42P (Feb. 9) 1935.

Dikshit has shown (1934) that intraventricular injections of acetylcholine produce cardiac irregularities and that this effect is probably produced by the action of the drug on centers in the hypothalamus. This suggested that the drug might also act on other hypothalamic centers, and its effect on the "sleep center" was investigated. Trephine holes were made in the skulls of cats under deep ether anesthesia, and the animals were allowed to recover. A week or more after the operation small doses of acetylcholine (from 0.1 to 0.5 micromilligram) were introduced into the lateral ventricle of the brain or deeper into the hypothalamic region. Such injections produced a condition closely resembling sleep. The effect came on from ten to thirty minutes after the injection and lasted for from two to three hours. Control injections of physiologic solution of sodium chloride produced no definite effect, while injections of 0.1 mg. of pilocarpine nitrate caused excitation.

ALPERS, Philadelphia.

EXPERIMENTAL ATONY PRODUCED BY BARBITURATES. DIVRY and EVRARD, J. belge de neurol. et de psychiat. **35**:170 (March) 1935.

Divry and Evrard studied decerebrate cats and rabbits that were given injections of a series of barbital derivatives. They conclude that intravenous injections of barbiturates will diminish and sometimes abolish the postural tonus of a decerebrate animal. The tendon reflexes are preserved, and the cutaneous mucous reflexes undergo pronounced diminution. They believe that this atony is produced by the action of the hypnotics on the central mechanism of tonus.

WAGGONER, Ann Arbor, Mich.

POSTACCELERATORY INHIBITION. B. KISCH, Arch. f. d. ges. Physiol. **235**:700, 1935.

In the heart of the frog that is overfed with potassium or calcium a postacceleratory inhibition is observed. This inhibition affects the formation of stimuli as well as the conduction of impulses. It can also be observed on the atropinized heart. It is assumed that the phenomenon is due to exhaustion.

E. SPIEGEL, Philadelphia.

ACTION POTENTIALS OF THE LATERAL NERVE IN STIMULATION OF THE LATERAL LINE ORGANS IN FISHES. H. SCHRIEVER, Arch. f. d. ges. Physiol. **235**:771, 1935.

The lateral line organs respond to constant stimuli by rhythmic impulses. The action potentials are relatively small (from 20 to 30 microvolts). On mechanical stimulation the threshold is very low, the excitation has a short latent period and the after-effect is short or is absent. If constant pressure is applied, adaptation soon occurs. On repeated application of pressure the lateral line organs become slightly fatigued. The lateral line organs react to chemical stimuli such as acids or salts; the adequate stimulus, however, is mechanical. These organs resemble the pressure sense organs of the skin in functional activity, while their structure resembles the labyrinth. Schriever is inclined to accept the old view that the pressure sense organs and the labyrinth are related and that the lateral line organs are a transition between the two.

E. SPIEGEL, Philadelphia.

Cortical Action Potentials in Stimulation of the Peripheral Taste Organ. Bun-ichi Hasama, Arch. f. d. ges. Physiol. **236**:36, 1935.

Various stimuli (5 per cent sodium chloride, 6 per cent sugar, 2 per cent sulfuric acid and 0.05 per cent quinine sulfate) were applied to the tongues of rabbits, and the cortical potentials were recorded. These stimuli induced an increase of the potential waves from an area of the lobus hippocampi behind the olfactory centers. Weaker changes in potential were recorded from a zone that extended from the lobus hippocampi dorsally to the corpus callosum and also from a zone between the lobus hippocampi and the occipital area. There was no specific relationship between the nature of the stimulating solution and the type of changes in potential. The amplitude of this change varies with the concentration of the solution, following an approximately logarithmic curve. Injection of strychnine increases and local application of cocaine on the tongue decreases the sensitivity of the taste organs.

E. Spiegel, Philadelphia.

Severance of All Semicircular Canals in Pigeons. E. Huizinga, Arch. f. d. ges. Physiol. **236**:52, 1935.

All the semicircular canals were severed in ten pigeons. The animals could fly normally and could even be used as carrier pigeons. Thus the loss of the semicircular canals as receptors for angular acceleration can be compensated, and the orientation of carrier pigeons may remain preserved. In the animals that were operated on tonic reflexes acting on the muscles of the neck could still be elicited from the cristae.

E. Spiegel, Philadelphia.

Acoustic Stimulation of the Vestibular Apparatus. G. V. Békésy, Arch. f. d. ges. Physiol. **236**:59, 1935.

By means of a model of the internal ear it was shown that acoustic stimuli may induce whirl movements of the perilymph. Pressure on the wall of the membranous labyrinth results and is transmitted to the otoliths thus causing disturbances in equilibrium. Such disorders in equilibrium were observed in normal men if the sound pressure was above 100 dynes per square centimeter. Synchronous oscillations of the head were observed when vibratory tones from three to five vibrations per second were used. Deviation of the head was produced by gradually decreasing tones.

E. Spiegel, Philadelphia.

Regulation of Temperature and Production of Fever in Homothermal Animals After Operations on the Central Nervous System. Rudolf Thauer, Arch. f. d. ges. Physiol. **236**:102, 1935.

The cervical portion of the spinal cord was severed in rabbits, and the animals were kept alive for two and a half months after operation. Immediately after the operation the animals were thermolabile, but not poikilothermic. The initial thermolability soon disappeared. From six to eight days after operation, the rabbits could be kept at room temperature and later at temperatures of 4.5° C. without decrease of their body temperature. Several weeks after operation the animals reacted to increased external temperatures like normal rabbits. While Freund and Strasmann concluded from their observations in acute experiments that the temperature regulation after transverse section of the cervical portion of the spinal cord differs from that after section of the thoracic portion, such differences were not found in Thauer's chronic experiments. The temperature regulation which reappeared after section of the cervical portion of the spinal cord persisted also after subsequent total extirpation of the spinal cord, severance of the cervical sympathetic nerve or subphrenic vagotomy. It is concluded that after elimination of all impulses arising in the central nervous system, the ability to regulate the body temperature is retained by the peripheral mechanisms. The experiments showed, furthermore, that true fever may develop after the supraspinal centers are disconnected from the lower parts of the nervous system.

E. Spiegel, Philadelphia.

Neuropathology

SERPENTINE ANEURYSM OF THE INTERNAL CAROTID ARTERY, WITH RESULTING ENCEPHALOMALACIA AND CEREBRAL HEMORRHAGE. OTTO SAPHIR, Arch. Path. **20**:35 (July) 1935.

Anomalies of the circle of Willis with resulting interruption of the circulation between the internal carotid and the vertebral arteries may form the basis of encephalomalacia and cerebral hemorrhage. Saphir describes three instances of encephalomalacia and cerebral hemorrhage, the cause of which was found in occlusion of the internal carotid arteries. The three instances recorded were significant because of the severe occluding lesions in the internal carotid arteries in locations where such lesions as a rule are not looked for, namely in the region of the cavernous sinus and within the carotid canal of the temporal bone. Narrowing of the lumen was also present in the first portions of the internal carotid arteries, in the pharyngeal region. The encroachment on the lumen was the result of tortuosity of the vessels with inversion of parts of their walls and the formation of bends or kinks. The tortuosity of the arteries is referred to as cirsoid aneurysm.

Saphir states that in every instance of encephalomalacia and cerebral hemorrhage the internal carotid and vertebral arteries should be carefully examined throughout their course in order to locate morphologically demonstrable causes of the lesions of the brain. Three procedures should be observed in the explanation of these lesions in the absence of occlusions of the vessels at the base of the brain or of their branches. 1. The internal carotid and vertebral arteries should be examined throughout their course for occluding lesions. 2. Congenital anomalies of the circle of Willis should be sought. 3. Morphologic evidence of cardiac failure, such as coronary arteriosclerosis with resultant myocardial fibrosis and chronic passive hyperemia of the various organs, should be looked for. All these anatomic lesions should be carefully evaluated or eliminated before the pathologist resorts to an explanation based primarily on functional disturbances.

WINKELMAN, Philadelphia.

THE ACTION OF ELECTRIC SHOCK ON THE NERVOUS SYSTEM. L. MARCHAND and JEAN PICARD, Encéphale **30**:229, 1935.

Less is known about the sequels of electric shock than about those of any other type of trauma. Mental disturbances due to electric shock are probably often not attributed to their true cause on account of the long period of latency and the frequent retrograde amnesia seen in persons subjected to this type of trauma. Permanent severe manifestations referable to the brain are rare. Naville and Morsier (1932) found neurologic symptoms lasting more than a few weeks in only 30 of 300 persons subjected to electric shock. They maintained that no proved case of permanent psychosis or dementia due to electric shock by industrial currents has been observed. Yet authors have reported personality changes with epilepsy ending in complete dementia after shock by a high tension current (Jellinek, 1934) and atypical chronic hallucinatory psychosis after shock of fifteen minutes' duration by a 200 volt alternating current (Schiff, Picard and Pouffary, 1927). In many such cases the rôle of the electric current is difficult to estimate and may be limited to revealing a previously existing condition; or else the trauma may be complex, as when a fall from a height accompanies the electric shock.

The pathologic anatomy of the sequels in the brain after electric shock received scant attention. The patient whose case is reported here was struck by lightning in 1928, at the age of 64. There was no history of any previous pathologic condition. Immediate effects were a burn of the left cornea and perforation of the left tympanic membrane. After transitory coma, he was inactive and listless. One year later, in May 1929, after a period of agitation, he was committed to an asylum, where intense anxiety, disorientation for time and space, incoherence, hallucinations, deafness, tremor and dysarthria were noted. Some improvement in the mental state permitted the patient's release in April 1930. Soon, however,

the symptoms reappeared, this time with a predominance of delusions of persecution. Voices threatened to cut his throat. Tendon and pupil reflexes were normal. There were no disturbances of motility, sensation or equilibration. There was no sign of localization of the lesion. The Wassermann test of the blood was negative. From this time on the mental condition remained unchanged. Signs of carcinoma of the stomach appeared, and the patient died of pneumonia in December 1933.

Necropsy showed extensive adhesions of the meninges to the cranium. The brain weighed 1,300 Gm. Histologically, the arachnoid showed thickened zones formed by imbricated and whorled layers of slightly flattened, finely fibrillar cells, without collagen, resembling certain meningoblastomas. There was a diffuse gliosis of the cortex. Neuroglia cells were present in groups of 5 or 6. The ganglion cells were atrophied and misshapen and contained a zone of pigment. The neurofibrils and a few chromidia persisted in the portions unoccupied by the pigment. The protoplasmic processes were much reduced. The nuceli were relatively little altered. Satellitosis was absent. The tangential fibers were much diminished and the stria of Baillarger only slightly apparent. There were no senile plaques. Numerous foci of mucocytic degeneration were present in the cortex and subjacent white matter. A few blood vessels were surrounded by embryonic cells and granular bodies stuffed with pigment. The basal ganglia, the thalamus, the bulbar olives, the cortex and the dentate nucelus of the cerebellum presented the same lesions of the ganglion cells and mucocytic degeneration. The nuclei of the cranial nerves were intact. The ependyma and the choroid plexus were unaltered.

No doubt could be entertained concerning the etiologic rôle of the electric trauma in this case. Indeed, the psychosis began immediately after a violent fulguration. A diagnosis of senile dementia could be ruled out by the absence of any history of deterioration previous to the accident and by the absence of the parenchymatous and vascular lesions of the senile type in the brain.

LIBER, New York.

Psychiatry and Psychopathology

EFFECT ON THE SKIN OF EMOTIONAL AND NERVOUS STATES: ETIOLOGIC BACKGROUND OF URTICARIA WITH SPECIAL REFERENCE TO THE PSYCHONEUROGENOUS FACTOR. JOHN H. STOKES, GEORGE V. KULCHAR and DONALD M. PILLSBURY, Arch. Dermat. & Syph. **31**:470 (April) 1935.

Stokes, Kulchar and Pillsbury made a special study of 100 patients with urticaria. About half of the patients were studied during a period of intensely competitive prosperity and the other half during an era of economic depression. The stresses and strain of the one period seemed as productive of psychoneurotic difficulties as the other. The disease appeared to affect twice as many women as men and for the most part seemed to be a disorder of early adult life. Sixty per cent of the family histories disclosed an "allergic-neurogenous" background. Only a small number (18 per cent) of the patients had symptoms referable to the gastro-intestinal tract. Focal infection was present in about half the cases, but evidence of the etiologic importance of these infectious foci was inconclusive.

In each case an appraisal of the psychogenic factors was made by Stokes. In 80 of 97 cases, psychogenic factors were operative either exclusively or in combination with other factors. A parallel series of control cases of cutaneous diseases other than urticaria was studied for comparison. The dominant influences in the psychoneurogenic background are given by the authors as "high tension," "neuroticism" and "chronic worry." These three factors were found in almost every patient presenting any psychogenic factor, whereas overt sex maladjustment was infrequent (4 cases only), and feelings of inferiority even more rare (3 cases only). The authors describe the urticariogenic personality as the "driving, high tension, competitive person, keyed to high pitch, and perpetually intent on destination, achieved at no matter what expense."

DAVIDSON, Newark, N. J.

THE DEVELOPMENT OF CHARACTER. FERDINAND BIRNBAUM, Internat. J. Individ. Psychol. **1**:67 (April) 1935.

Each child is born with an impulse to dominate. The resistance which the environment sets up to the consummation of this impulse constitutes a conflict, the solution of which is expressible in terms of the child's relationship to society. The child may seek to solve this problem by evading it, by withdrawing into isolation; he may seek to dominate the family, or he may identify himself with an outlawed community, the gang. In each case he will set up some community as his frame of reference and seek to express himself within that framework. The ultimate goal is often a fantom, the unreality of which the child may recognize but the potency of which is irresistible. The courageous person adjusts this fiction in accordance with the social realities; the discouraged person fails to do so.

The so-called "behavior disorders" are merely bids for recognition in which the child exploits any organic inferiority that may be present. The "weak stomach" or the "weak bladder" gives rise to nervous vomiting or enuresis. The therapeutist, whether teacher or psychiatrist, must appear to the child as the representative of the integrated community of the outside world. Through him the patient must see glimpses of the wide world beyond the family. To the child the therapeutist must reveal the shabby nature of the limited type of dominance which he is achieving by his conduct disorder and contrast it with the glamor of attaining distinction in the outside world.

DAVIDSON, Newark, N. J.

DEPRESSION AS A PART OF A LIFE EXPERIENCE: STUDY OF FORTY CONSECUTIVE CASES. NIELS L. ANTHONISEN, J. A. M. A. **105:** 1249 (Oct. 19) 1935.

Anthonisen observed forty consecutive patients (thirteen men and twenty-seven women) with depressive states. All were less than 50 years of age. Several of the patients had had attacks before, and an attempt was made to bring those attacks inside the sphere of the investigation. The investigation embodies a study of the prepsychotic personality, the etiology of the depressive states in terms of more topical predisposing factors and the course of the illness. The information given concerning the prepsychotic personality of the patients indicated that thirty-one had had difficulties in socialization due to sensitiveness, shyness and awkwardness, at times coupled with irritability, intolerance and aggressiveness. One patient was sociable but overanxious to please all people, and two other patients were regarded as sociable but extremely egotistical and indulged. The difficulties of these thirty-four patients were reflected in their activities. It is traditional to consider "spontaneous" mood swings as being characteristic of the manic-depressive psychosis. In only one case was it stated by one of the relatives that the patient had been happy or depressed "without reason." The patient himself felt that his mood swings had been dependent on events of an encouraging or a discouraging nature. It seems to the author more correct to regard such types of patients as extraordinarily susceptible to depressive reactions, so much so that life only occasionally holds encouraging and hopeful experiences, rather than to consider them constitutionally and unconditionally depressed. The depressive tendencies were all found in patients who had shown difficulties in socialization. The depressive mood has its inception with the anxiety and tends to protract and to emphasize it. The information received concerning the six remaining patients indicated that in their setting of life they had enjoyed a satisfactory adjustment. It was only their psychoses that brought out their narrow margin of adjustment and dependence on certain conditions. With these changed, a few of them had difficulties in regaining even a tolerable adjustment. Little knowledge was gained as to the influences that had helped to bring out the traits in the forty patients. In only two cases was it not possible to point to significant etiologic factors of the depression, besides the personality factor. One of these patients refused to give information. The other patient was vague and hesitant, and in both cases objective information was lacking. In a considerable number of cases, excluding those in which the condition occurred during the puerperium, physical illness was a com-

plication. The "motifs" of the precipitating factors represented in the main complaints could be followed more or less clearly through the illness in twenty-seven of the forty cases. Of particular interest was the study of the frequently occurring self-depreciation and self-condemnation. The complaints were accordingly an estimation of the situation in which the patients found themselves with regard to their relations to other people, their capacities and worthiness, their failures and their outlook. In a few cases their problems were actually solved with the hospitalization, as burdensome responsibility was thereby removed automatically. In all the cases, twenty-three in number, in which considerable improvement, a comfortable hospital adjustment or recovery occurred, important changes took place in the relationship between the patient and the environment. In none of these cases was there a "spontaneous" improvement, if by "spontaneity" one means an improvement without fulfilment of a certain need of the patient, that is, without a new outlook. A new outlook was brought about either by change in the situation or by an alteration of the patient's own attitude, compared with his prepsychotic attitude. In the four unimproved persons and in part in those who made a hospital adjustment there was an incapacity to utilize the opportunities of environmental changes or to change their attitudes to the unchanged environment. This was due not to the depressed mood as such but to the personality make-up. There was thus a correspondence between prepsychotic personality, the nature of the precipitating factors of the psychosis and the outcome. Character traits, such as flexibility or rigidness, docility or demanding aggressiveness, and insecurity or relative self-sufficiency, were reflected in the psychosis and determined, in conjunction with the therapeutic resources, the duration and the final outcome.

EDITOR'S ABSTRACT.

JUDICIAL VERSUS ADMINISTRATIVE PROCESS AT THE PROSECUTION STAGE. W. A. WHITE, J. Crim. Law & Criminol. **25**:851 (March) 1935.

It appears to some that the machinery of law enforcement is breaking down. The difficulty is an old one and cannot be solved by hastily devised plans. The approach of the physician is different from that of the lawyer. The former is primarily interested in the individual, while the latter is interested in the act. Because of the development of the law some observers have believed that there is little hope of doing anything along lines of changing the legal system. Nevertheless, improvements in the system, such as psychiatric services, special departments for juvenile delinquents and improved classification of prisoners, are all indicative of some progress. One of the most noticeable advantages in the extrajudicial methodology of law enforcement is the Briggs Law, which undertakes to determine the responsibility of the offender in terms of his mental status. A board of experts to advise the courts has also been considered. Institutions that deal with the offender should do so not to collect material for a filing cabinet but to improve the status of the offender. White believes that the individualistic point of view of the psychiatrist and the social point of view of the legalist will meet and face common objectives.

SELLING, Detroit.

PSYCHOLOGICAL MALADJUSTMENT IN COLLEGE AND IN LATER PLACEMENT. ELISABETH M. SULLIVAN, J. Nerv. & Ment. Dis. **82**:147 (Aug.) 1935.

Sullivan finds symptoms of five classified disorders in college students, namely, psychoneurosis, psychopathy, manic-depressive psychosis, schizophrenia and epilepsy. Psychologic maladjustment arises most frequently from the student's own reaction to a complex family situation or to an inner personal conflict.

HART, Greenwich, Conn.

A Mental Hygiene Clinic in a High School. An Evaluation of Problems, Methods and Results in the Cases of 328 Students. Marian McBee, Ment. Hyg. **19**:238 (April) 1935.

After a study of the case records in a mental hygiene clinic associated with a good high school in a middle class neighborhood, McBee classifies behavior problems of adolescence into four groups, those associated with scholarship, truancy and personality, respectively, and a miscellaneous group. The last group included some instances of delinquency and some of conduct disorders based on physical disabilities. Among the children of foreign-born parents, a disproportionate number of personality problems was found, owing in part to the clash between the foreign culture of the parent and the Americanized standards of the children. This clash tends to produce either shyness or overaggressiveness. Further studies show that more careful placement of pupils and more experience with self-reliance are needed in the elementary schools of the community. Many difficulties arising from high school scholarships were found to be based on social or personality problems. The need for studying the student as a psychic unit, rather than by fragments, was stressed. Emphasis was also laid on the importance of adequate vocational guidance. The best time for the interview of the student by the social-psychiatric worker was found to be during the second year of high school, and the establishment of this procedure as a permanent routine is urged. The increasing use of the school clinic as a community mental hygiene center is suggested.

Davidson, Newark, N. J.

The Psychogenic Origin of Organic Disease. Eli Moschcowitz, New England J. Med. **212**:603, 1935.

The effect which mental processes may have in the production of organic disease is discussed. This can be observed best by the general practitioner, since the physician in a hospital or the specialist sees only a cross-section of the patient and misses the early stages of the disease. Moschcowitz mentions the theory of the continental school, which holds that morbid anatomic changes precede abnormal function. He suggests the term "psychnosia" to describe diseases of emotional origin.

The following diseases are treated in the article and are considered to originate in psychologic mechanisms: essential hypertension, exophthalmic goiter, gastric and duodenal ulcer, cardiospasm, spastic or irritable colon and mucous colitis. In evaluating the factors to be dealt with, the precipitating cause as well as the type of personality which the patient possesses must be considered. All the diseases mentioned pass through three stages of evolution: constitution, fixation of an exaggerated function of an organ or organs and development of the lesion.

The characteristics of diseases which may be included in the term "psychnosia" are that they may be physiologic in that there is an exaggeration of a normal function and that they are all human diseases. They rarely occur before puberty or the time of the development of the affective powers; they tend to recur, and they bear a relation to world crises or emotional worry. Psychiatric treatment is important in dealing with such diseases, but it is more effective if prophylactically applied.

Moore, Boston.

The Concept of Mental Deficiency in Theory and Practice. David Wechsler, Psychiatric Quart. **9**:232 (April) 1935.

Mental deficiency, involving not only a lack of intellectual skill but also an incapacity to apply intelligence to life situations, cannot be defined entirely in terms of an intelligence quotient, since the psychometric test at its best measures intellectual efficiency only and not really ability to apply intelligence. A case is cited in which a young man with an intelligence quotient of 91 had presented a persistent moral problem, was repeatedly antisocial and was apparently chronically unable to meet the ordinary requirements of adjustment to social life. This is

contrasted with the case of a native rural laborer with a mental age of 8 who made a good living, supported a family and was for all practical purposes a good, useful citizen. At least three types of mental deficiency must be defined: (1) emotional or moral deficiency, (2) social or vocational deficiency and (3) intellectual deficiency in the narrow sense of the phrase. DAVIDSON, Newark, N. J.

THE MENSTRUATION COMPLEX IN LITERATURE. C. D. DALY, Psychoanalyt. Quart. **4**:307, 1935.

Daly presents much material from Baudelaire's and Poe's works to illustrate his thesis that the nucleus of the incest barrier is the son's observation of the mother's vaginal bleeding and that the mother with a penis is a defense against the fear and dread of the bleeding woman, that is, the woman "in heat." She is feared and dreaded because she represents the confirmation of the little boy's fear of castration and death. PEARSON, Philadelphia.

ON DEPERSONALIZATION. W. MAYER-GROSS, Brit. J. M. Psychol. **15**:103, 1935.

Through the study of twenty-six patients with mental disease who complained of the depersonalization syndrome, Mayer-Gross attempted to gain further information by the introspective method, i. e., by the verbal descriptions of their conditions by the patients. There was little uniformity in the complaints. Some told of changes in the perception of space and some of disturbances in hearing; others told of bodily changes, loss of picturing, an increase or decrease in the rate of the passage of time, loss of emotions and disturbances of memory. The same symptoms may be present in various organic conditions, and the diagnosis of the mental conditions among these patients varied from depression to neurasthenia. Mayer-Gross concludes that depersonalization is a nonspecific preformed functional response of the brain occurring in various illnesses during the stage of minor intensity. It is always one and the same disturbance, similar to other nonspecific preformed mechanisms, such as epileptic fits, semiconsciousness and delirium. He suggests further study through the medium of refined methods for sensory perception. ALLEN, Philadelphia.

THE CATEGORIES OF THE APHASIC SPEECH AND THE SCHIZOPHRENIC DISSOCIATION. C. PFERSDORFF, Ann. méd.-psychol. **93**:1, 1935.

A comparison was made of the characteristic speech disturbances in cases of organic diseases and of schizophrenia. In both groups the disturbances occur most frequently in the domain of propositional speech. From the point of view of syntax, one finds in both groups (1) short grammatically correct sentences, but with single words distorted, and (2) long sentences of complicated structure, often incoherent and vague. The fundamental difference between the two diagnostic groups is that while the speech of aphasic persons is always meant to convey a definite idea, that of schizophrenic persons may take the form of automatic speech, which consists of sentences grammatically correct but deprived of all meaning. In conclusion, Pfersdorff touches on the problem of localization, reporting three cases of tumor in which there were disturbances of speech similar to those observed in cases of schizophrenia. MOORE, Boston.

CERTAIN ETIOLOGIC FACTORS IN DEMENTIA PRAECOX. A. COURTOIS, Ann. méd.-psychol. **93**:51, 1935.

The following data were obtained from 200 schizophrenic patients. In 65 per cent of the cases there was poor heredity on one or both sides of the family. Sixty-three per cent gave a history of encephalopathic conditions, such as delirious states, infantile convulsions and injuries to the brain, or of general diseases, such as tuberculosis. Neurologic symptoms were found in 23 cases only. They showed no relationship to the presence of the two factors mentioned. The cerebrospinal

fluid was slightly abnormal in 54 of 162 patients examined. Courtois points out the high percentage of foreigners (over 25 per cent), especially of Jews, in the group investigated. He concludes that dementia praecox is not an entity but may be produced by different etiologic factors.

MOORE, Boston.

BILIOUS ANXIETY. H. BARUK, H. BRIAND, L. CAMUS and R. CORNU, Ann. méd.-psychol. **93**:177, 1935.

Starting from the old theory of a bilious etiology of depressive disorders, the authors report three cases of hepatic dysfunction accompanied by depressive symptoms. The problem of bilious intoxication is also approached experimentally. It was found previously that injection of animal or human bile produced neurovegetative disturbances, especially of respiration, in experimental animals. In the present study bile was used that was procured from one of the patients with hepatic dysfunction who was in a state of anxiety. The authors expected this bile to have a greater neurovegetative toxicity. They succeeded in obtaining especially strong effects in the animals into which injections were made. In further experiments with solutions of bile salts the changes in respiration were registered graphically. While intravenous injections seem to slow respiration, subcutaneous injections only change the form of the respiratory curve. The authors conclude that since bilious intoxication can be shown to influence the vegetative centers, the hypothesis of the bilious etiology of some forms of anxiety is not altogether unfounded and deserves closer consideration.

MOORE, Boston.

THE RÔLE OF CHLORINE METABOLISM IN ANOREXIA AND SITOPHOBIA OF CERTAIN PATIENTS. MARES CAHANE, Ann. méd.-psychol. **93**:193, 1935.

Cahane found that some acutely psychotic patients who refuse food showed changes in the metabolism of chlorine. After this condition was removed by treatment, the appetite was restored. Some patients presenting loss of appetite but no indications of a disturbance of metabolism of chlorine were treated successfully in the same way. The author concludes that anorexia and sitophobia are dependent on certain vegetative centers which can be influenced by an unusual concentration within them of chlorine.

MOORE, Boston.

COLON BACILLUS PSYCHOSIS. HENRY HOVEN, J. belge de neurol. et de psychiat. **35**:127 (March) 1935.

Hoven has observed a series of cases in which mental symptoms were manifested in the presence of infection with the colon bacillus. In some the psychotic manifestations were present before the known infection. Treatment was apparently of no particular value in the relief of the psychosis. He believes, however, that certain patients who present psychotic manifestations show marked improvement or cure as a result of treatment of the infection.

WAGGONER, Ann Arbor, Mich.

CHEMISTRY OF THE PSYCHOSES: CLINICAL SIGNIFICANCE OF DISORDERS IN ACID-BASE EQUILIBRIUM. OTTO WUTH, Fortschr. d. Neurol., Psychiat. **4**:13 (April) 1933.

Three factors characterize the physicochemical milieu of the body: (1) the isotonicity of the tissues and the body fluids, i.e., the maintenance of balanced amounts of mineral substances; (2) isotonicity, or ion balance, i.e., the maintenance of the mixture relationship of the individual salts, and (3) isohydricity, i.e., the maintenance of an equilibrium of hydrogen ions and hydroxyl ions, or the acid-base equilibrium. The author discusses only the acid-base problem in its clinical relations, particularly in connection with psychiatric problems.

The actual acidity or alkalinity of a solution depends on the concentration of hydrogen or hydroxyl ions. Since a determination of the hydrogen ions is easier than a determination of the hydroxyl ions, in practice one determines the hydrogen ion concentration in order to find the acidity of a solution. The neutral point lies at p_H 7. Values over 7 show alkalinity; values below 7, acidity. The higher the concentration of hydrogen ions, the lower the p_H figure, and inversely. The p_H of the blood is about from 7.28 to 7.40; hence, the blood reacts with mild alkalinity. In autumn, according to Straub, stronger basic values are found; in the spring, stronger acid values occur; in connection with this attention is called to the seasonal variations in the frequency of certain diseases, such as eczema, tetany and psychoses, and to the occurrence of suicide. The latitude of reaction of the blood is strongly maintained and has regulatory functions. The latter are necessary because of the formation in the organism of acid and alkaline metabolic products. Regulation occurs not only through the buffer albumins but particularly through the expired air, urine, blood alkalis and gastric juice (intestinal phosphates). Excessive acid in the blood is bound mainly as carbonate; in the urine, as carbonate and phosphate; in the stomach, as hydrochloric acid, and in respiratory air, as carbonic acid. Carbonic acid circulates in the blood not only as free carbon dioxide and in a chemically bound form but in a dissociable form. All carbonates which are not bound by other acids are transformed into bicarbonates, and thus establish the so-called alkali reserve.

The regulatory mechanism by way of the urine is manifested by the salt content and by fluctuations in acidity. Thus, for example, after meals the urine is more alkaline; during sleep, it becomes more acid. To a certain extent there is a normal daily curve of acidity of the urine. Around 3 a.m. the urine shows its greatest acidity; in the morning it is still acid; after meals the acid content becomes reduced; it reaches its highest values during the night.

In acidosis and alkalosis there are relatively small deviations from the normal; large deviations are not compatible with life. A high acidity cannot develop because before it can occur all carbonic acid must have vanished from the blood; strong alkalinity cannot develop because through accumulation of bicarbonate an increase of osmotic pressure so great that the kidneys would not permit it would be necessary.

Various forms of acid-base disturbance are recognized. They are as follows:

1. Uncompensated alkali excess. This can be provoked by overdoses of sodium bicarbonate or by a prolonged loss of gastric hydrochloric acid. The bicarbonates of the blood (alkali reserve) are increased; the p_H is elevated. The clinical manifestations consist of increased neuromuscular excitability, which may be manifested as tetany or convulsions.

2. Uncompensated carbon dioxide. This condition likewise produces an alkaline reaction of the blood, with an elevation of p_H. The alkalosis is not provoked by a primary increase of bases but rather by a diminution of acids. The cause may be hyperventilation or high altitude. Since the result is the same as in uncompensated alkalosis, the clinical manifestations are the same.

3. Compensated $\frac{\text{alkali excess}}{\text{carbon dioxide excess}}$. In this condition there is a milder form of the conditions described under 1 and 6. Since the condition is compensated the p_H is normal. The amount of base is high even with excess of carbon dioxide; in order to balance and compensate for the excess of acid, an increase in the alkalis occurs. Compensated excess of alkali may follow an uncompensated excess of alkali such as is described in group 1; compensated excess of carbon dioxide may follow an uncompensated excess as described in group 6.

4. Normal acid-base equilibrium. This condition requires no comment.

5. Compensated $\frac{\text{alkali deficit}}{\text{carbon dioxide deficit}}$. In this group are milder forms of conditions described in groups 7 and 2. If carbon dioxide is lost the amount of base becomes secondarily lowered in order to reestablish equilibrium. Alkali deficit may occur as a result of attachment of alkalis due to increased acid;

increased acid may have origin in increased formation of acid (diabetes) or in delayed excretion of acid (nephritis). The causes of carbon dioxide deficit may be oxygen deficiency, high altitudes and hyperventilation.

6. Uncompensated carbon dioxide excess. Since carbonic acid accumulates and no compensation occurs, the p_H is lowered and acidosis exists. The causes may be inhalation of air with from 3 to 5 per cent carbon dioxide or reduction of the excitability of the respiratory center, e.g., in morphine narcosis.

7. Uncompensated alkali deficit. In this condition the blood alkali is reduced; since no compensation exists the p_H shows a reduction. This may occur just before death in nephritis and diabetes or in deep ether narcosis.

The deviations that occur in the body fluids in association with acidosis and alkalosis are as follows:

Acidosis	Alkalosis
Retardation of metabolism	Acceleration of metabolism
Hyperglycemia	Hypoglycemia
Low alkali reserve	High alkali reserve
Low p_H	High p_H
Leukopenia	Leukocytosis
Urinary ebb and flow	Lymphopenia
Low urinary p_H	Diminished amount of urine
Urinary phosphate increased	High urinary p_H
High NH_3 values in the urine	Diminished urinary phosphates
Urinary nitrogen diminished	Urinary nitrogen increased

In neuropsychiatric conditions more or less severe acidosis is found in all states of malnutrition as well as in severe motor excitement, because in these disorders there is an overproduction of the acid products of metabolism. There is often a reduction in the alkali reserve of the blood, with the clinical manifestations associated with acidosis. In cases of malnutrition and excitement acidosis arises from increased production of the acid products of metabolism. In the stupor conditions of manic-depressive psychosis and in schizophrenia it in all probability arises from a psychic disturbance of respiratory activity. Respiration in patients who are huddled up in a cramped position is often superficial, ventilation is inadequate, an accumulation of carbonic acid occurs; there then arises an acidosis with an associated disorder of the vegetative nervous system. Further evidence of this is seen in subnormal temperatures, slowing of the pulse, cyanosis, pseudo-edema, gastro-intestinal disturbances and the reduction in gas metabolism.

Alterations of respiration, which in turn find expression in changes in the acid-base balance, seem to play a rôle as yet too little observed in psychoses and neuroses. Investigations of the hydrogen ion concentration of saliva (dental caries) have shown that a higher degree of alkalosis exists in the psychoses, particularly in those of affective types, as well as in the neuroses and in certain forms of stuttering. It is less true of schizophrenia. This effect is often seen in the urine. This increased alkalosis obviously is based on hyperventilation with loss of carbon dioxide. An increase in hyperventilation produces the disease picture of neurotic respiratory tetany and postencephalitic attacks of respiratory tetany.

The problem of epilepsy was attacked along similar lines. Bigwood and Vollmer came to the conclusion that alkalosis is the cause of convulsions in cases of epilepsy. Förster succeeded in producing convulsions in epileptic persons by creating alkalosis through hyperventilation. The increase in calcium ionization with its effect in increasing excitability is also a factor in epilepsy. Paradoxical anoxemia, described by Haldane and Henderson and induced by alkalosis, may likewise be a factor. This consists in the oxygen being so firmly attached to the hemoglobin that it cannot be given off to the cell though sufficient oxygen is available. The cell asphyxiates, so to speak; the brain cells, being the most sensitive, should be first affected, a situation which, for example, occurs in the unconsciousness and convulsive attacks associated with heart block, through interruption of the blood supply to the brain.

With these findings and the theories based on them, it was thought that a definite step was made toward elucidating the problem of epilepsy. However, preparoxysmal alkalosis cannot always be established in cases of epilepsy. Convulsive attacks can be released by creating an alkalosis by means of hyperventilation in only about 40 per cent of cases. Bigwood's figures for calcium, according to which a repression of calcium ionization occurs, were not obtained by experiment, but were calculated on the basis of hydrogen ion concentration. Finally, according to Wuth the blood content is normal as to free and ionized calcium. Whereas in tetany the alkalosis, especially the disorder of the calcium fraction associated with it, seems to play an important rôle, this is not so in the majority of cases of epilepsy. The close relations between tetany and genuine epilepsy seem not to exist from the metabolic chemical standpoint to the degree previously assumed. The situation appears to be that in epilepsy alkalosis represents one of the numerous ways in which convulsions may occur in the sense of a nonspecific increase of neuromuscular excitability, which may be manifested not only in epilepsy but in other organic nervous disorders.

Among other states of alkalosis with convulsions is pylorospasm in which the alkalosis occurs as a result of prolonged loss of gastric hydrochloric acid. Convulsions with acidosis occur in cardiac disorders, pneumonia, asphyxiation, fever, diabetic and uremic and certain exogenous toxemias.

The sequelae of the epileptic attack are determined by increased motor activity and well marked acidosis. This acidosis arises first from a limitation of breathing and hence from an accumulation of carbonic acid; second from the increased formation of the acid products of metabolism associated with muscular activity, the oxidation of which in turn is hindered by the carbon dioxide acidoses and the excretion of which is inhibited by spasm of the blood vessels of the kidneys. This acidosis is characterized by changes in the blood picture, for example, displacements in the albumin-globulin relationship, the excretion of an acid urine with many phosphates and ammonia, the excretion of acetone and lactic acid and an increased excretion of gastric hydrochloric acid, which is probably compensatory. The entire postparoxysmal disease picture is in a measure dominated by acidosis.

Many authors consider sleep a state of acidosis associated with vagotonia. According to Straub, many manifestations of sleep may perhaps be explained as secondary elaborations of acidosis. These relationships are still in no way entirely clear. Undoubtedly they play a part in many neuroses, and perhaps later they may gain important therapeutic significance. A ready example is found in the gastric and intestinal neuroses in vagotonia with hyperacidity and spasms, in which the spasms and the hyperacidity may be stopped either through conversion of the vegetative tonus with atropine or foreign protein therapy or through combating the hyperacidity with alkalis alone.

As regards the effects of useful pharmaceutical preparations on the acid-base equilibrium, Wuth has begun to investigate various hypnotic drugs; hypnotics belonging in various chemical groups seem to behave differently in their effect on the acid-base equilibrium. Some cause alkalosis (ethyl carbamate) [urethane]; others, like paraldehyde, cause acidosis. Alcohol in single doses produces a stronger acidosis than paraldehyde; perhaps it exerts a stronger effect on the respiratory center. The sequelae of acute alcoholic poisoning and the so-called *Katzenjammer* states generally seem to be associated with fluctuations in acid-base equilibrium, with changes in tonus in the vegetative nervous system and fluctuations in the ion balance; this is supported in part by investigations and in part confirmed by the results of therapy, namely through the good effect of remedies which have a sedative effect on the vegetative nervous system as well as intravenous or oral administration of acids or table salt.

Related to these disorders probably are the morbid manifestations of withdrawal of morphine. The acid-base equilibrium in chronic morphinism seems to show marked deviations from normal of a type different from that produced by a single dose. In Wuth's experience acidosis seems to develop frequently with the symptoms following acute abstinence from morphine, this may represent the cause of the

deliria, collapse or come which sometimes develop when the symptoms are severe. Undoubtedly severe disorders in the vegetative-endocrine system are present in morphinism. One may say that morphine essentially depresses the sympathetic nervous system and the glands which correlate, enhance and accelerate it (thyroid and adrenal) and that this depressing effect is reversed into the opposite condition of overexcitability during withdrawal. Therefore the withdrawal symptoms can be made milder, experimentally and therapeutically, with sympathetic-depressing remedies, like those of the antipyrine group, through vagus-stimulating substances like choline, or through conversion of the vegetative tonus by means of foreign protein therapy. Wuth was the first to call attention to the antithesis of the vegetative endocrine symptoms in periods of habituation and abstinence. In the first one sees dry, atrophied skin; trophic disturbances of the hair, teeth and nails; contracted pupils; reduction of glandular secretion and amount of urine; impotence; cessation of menstruation and psychomotor rest. In periods of abstinence, on the contrary, there are warm moist skin, dilated pupils, increased glandular secretion, diarrhea, flow of saliva, increased libido, disturbances of respiration, psychomotor restlessness with anxiety and, what is particularly emphasized, hyperacidity of the gastric juice. Contrasting changes in metabolism and blood composition go hand in hand in these disorders. If one places these symptoms side by side, they recall the contrast of the symptoms in hypothyroidism and hyperthyroidism. Indeed, many of the symptoms of habituation correspond with those of states of hypothyroidism; many symptoms of abstinence are similar to those in thyrotoxicoses. Experimental pharmacology lends further support to this assumption. It has been shown, for example, that white mice become more sensitive to morphine through administration of thyroid; they show severe symptoms and die sooner. The metabolism of dogs habituated to morphine behaves like that of thyroidectomized dogs; in both kinds of dogs the metabolism is increased through thyroid, and both types of dogs are insensitive to oxygen deficiency. The latter is probably determined through the effect of morphine on the respiratory center, as the excretion of carbonic acid is disturbed thereby there occurs also a disorder of acid-base equilibrium. Undoubtedly the individual symptoms of periods of habituation to and abstinence from the use of morphine are to be traced not only to the direct depressing effect of morphine on the tonus of the entire vegetative nervous system, especially the sympathetic nerves and the glands like the thyroid and adrenal which correlate and accelerate it, but also to the disturbance of acid-base equilibrium.

BOLTZ, Binghamton, N. Y.

COLLECTIVE PSYCHOTHERAPY. M. MÜLLER, Fortschr. d. Neurol., Psychiat. **7**:330 (Aug.) 1935.

Collective psychotherapy finds its best applications in the field of the psychoses rather than in the field of the neuroses. In the psychoses, the forsaking of reality is expressed differently than in the neuroses. The psychotic person is individualistic; he lives in his own world and is unsocial or even aggressive toward the real one. It is possible to approach the reintegration of the psychotic person through the use of individual psychotherapy, but in accord with the principles of mass psychology the attempt is influenced favorably when the patient feels himself one of a number of other persons who are being led in the same direction.

The author reviews the work of Simon, who after study of the methods of collective psychotherapy hitherto employed in psychiatric institutions, reached the negative conclusions that the older institutional routine is distinctly inadequate if not actually harmful. Simon deplored particularly the nihilistic attitude assumed by many physicians when faced with a patient with a major psychosis and the attitude of resignation and sense of irresponsibility thus fostered in the patient himself. The concept of the hopelessness of the psychoses has perhaps sprung from the general conception of a psychiatric hospital as a place of forbidding stone walls, grated windows, bare, cold rooms and censored mail, in which live not human beings but "inmates," like condemned criminals expiating for a life of sin. And

what other conclusions can the patient himself draw when, despite all the kindness with which he may be treated, the cell-like rooms, rough immovable furniture, tin utensils, institutional clothes and locked doors remind him how closely he is guarded and how much he is mistrusted? Further, how can he avoid being unfavorably influenced by the disturbing sights and unceasing din of the usual "asylum?" Is it any wonder, then, that he soon gives up all sense of responsibility and retreats further and further into his psychosis until he is irretrievably withered in body and in mind?

It may, of course, be stated that the preceding criticisms of Simon have long been common knowledge; it has likewise been conceded that any improvement of psychiatric institutions will have to come slowly. Simon, however, advanced this constructive postulate: Every psychotic person, even if apparently irrevocably deteriorated, can yet respond to therapy if only he is not regarded as hopeless and irresponsible. He must be taught that even in his institution he has not only rights but duties and that he must work according to his ability and talents and must not, in his leisure, retreat into inactivity, lethargy or stupor.

This principle of therapy, to be effective, must pervade all the personnel of an institution, from director to scullery maid, who have anything to do with the patient. This requires the selection of a trained, intelligent, cooperative staff, capable of guiding favorably almost every moment of the patient's stay in the institution. The patient's life must be so ordered that every contact he makes with physicians, nurses or other patients is either harmless or definitely stimulating and favorable. The patient should never be allowed to regard any form of treatment as punishment; it must be considered simply as a logical result of his own actions. Objectionable mannerisms and stereotypes of the patient may be overcome by repeated reassurance and objective retraining. Thus, a degenerated senile woman who for years had been in the habbit of scratching her face and tearing her hair, desisted only after a nurse had spent two days with her urging her to stop her harmful activity and operate a loom instead. Within eight days the patient was constantly busy at her loom and refused even to speak of her previous habits.

According to Simon, occupational therapy is of great importance and should be employed for from 80 to 90 per cent of institutional patients. However, the work must be so individualized as to increase self-respect and stimulate motives for recovery and must not be routine and monotonous. There need be no form of occupation about an institution which the patients cannot be trained to do, while at the same time they are taught a trade and acquire self-reliance, a sense of duty and habits of industry. The patient, if it is desired, may even be recompensed by a form of hospital currency, with which he can purchase little luxuries for himself from the products of other patients. By these means, a spirit of competitive esprit and camaraderie can be built up. In his free time the patient should be encouraged to read current periodicals and to join in dances, theater and cinema parties and other social activities. A spirit of group pride in the patients may also be fostered by improving the physical aspects of the institution: Bleak wards and forbidden grounds should be converted, respectively, into cheerful work and recreation rooms, gardens and pleasing landscapes. By the general application of this so-called "reactivating psychotherapy" of Simon, the formation of artificial symptoms arising from the older types of institutional life can be avoided, and many apparently advanced psychotic processes can be halted or reversed.

As to exactly how these methods of therapy benefit the individual patient there may, however, be some controversy. Aside from the beneficial physical influences of work in the fresh air and consequently increased motor and circulatory activity, it is probable that the most potent factor in bringing about recovery is the realization by the patient that he is regarded as a responsible human being of whom self-control and personal and social readjustments are to be expected.

The dangers of the reactivating therapy of Simon are minor but should not be neglected. One possibility is that the scheme may be oversystematized and the patient made to lose his individuality. Another is that special investigations into

specific etiologic factors and individual psychotherapeutic procedures in the various psychoses may be neglected. A third possibility is that if institutional life is made as varied and satisfying as indicated by the principles of reactivating collective psychotherapy, many patients will respond but will remain permanently attached to the institution and unable to face the real demands of life outside it. This tendency, however, may be overcome by a graduated resumption of full extramural life through stages of placement in individual wards, foster families and other controlled environmental readjustments.

MASSERMAN, Chicago.

SCHIZOPHRENIA IN EARLY CHILDHOOD. E. GREBELSKAJA-ALBATZ, Schweiz. Arch. f. Neurol. u. Psychiat. **34**:244, 1934; **35**:30, 1935.

In twenty-two cases of schizophrenia studied, the patients' ages ranged from 3½ to 8 years, and the period of observation, from six months to three and one-half years. A brief history is given in each of the nine cases with an acute onset. Hereditary taint was generally lacking in this group, and the children seemed to have been normal prior to the appearance of the psychosis. With one exception, the ages of the children at the onset of the disease fell between 2½ and 3 years in all nine cases. Anxiety states, motor unrest, disturbed sleep and dulling of affect with loss of former attachments were frequent early symptoms. Negativism, stereotyped actions and other manifestations of catatonia were observed. Two of the children had definite hallucinations, and the behavior of two others indicated that they were hearing voices. The further course was characterized by deterioration of the personality with intellectual defect of varying degree. In the author's words: "The further development of these children is extremely unproductive."

In the remaining thirteen cases it was impossible, with one exception, to determine the age of the patients at the onset of the psychosis. Anomalies of development were noted in nine instances, and, in contrast to the first group, schizophrenia was of frequent occurrence in the antecedents. Disturbances in thinking, ambivalence, apathy, dulling of affect and other emotional peculiarities were characteristic symptoms. The normal interests of childhood were generally lacking. The children were in much poorer physical condition than were those in the first group; stigmas of degeneration and vasomotor changes were common. The course, in general, was slowly progressive, with intellectual impairment, difficulties of adjustment and change in personality, although deterioration was less marked in this group.

DANIELS, Denver.

STATISTICAL STUDY OF HEREDITARY TAINT IN A SELECTED GROUP: SIBLINGS AND PARENTS OF 362 OFFICERS AND INMATES OF A HOSPITAL IN SAXONY. BERTHOLD BERLIT, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:622 (May) 1935.

Berlit reports a study in which an attempt is made to estimate the incidence of mental disease in a control group of patients. In order to evaluate the data collected in the study of the genetics of mental disease, it is necessary to know the incidence of mental disease, personality and character defects, mental deficiency and epilepsy in control groups. The author chose the employees of a hospital for patients with mental disease as the control group because of their willingness to cooperate and their relative reliability concerning the incidence of mental disease in relatives. In estimating the incidence of a particular disease relatives alone were included who were within the age group during which that disease is known to occur. The frequency of psychopathy, for instance, was determined in those over 10 years of age and of hysteria in those over 5.

In studying 1,807 siblings he found the following percentages of incidence of various diseases: dementia paralytica, 0.41; schizophrenia, 0.79; epilepsy, 0.41; mental deficiency, 0.62; hysteria, 0.41; psychopathic personality, 2.4; psychopathy-like states, 4.8; alcoholism, 0.08; suicide (without psychosis), 4.6; mortality from tuberculosis, 24.1. One and thirteen hundredths per cent of the siblings had wandered away and were not located.

In 724 parents the following percentage incidence of abnormal mental states was found: schizophrenia, 0.15; manic-depressive psychosis, 0.47; dementia paralytica, 0.15; senile psychosis, 0.95; mental deficiency, 0.13; hysteria, 0.27; suicide, 1.3 (without psychosis); alcoholism, 0.41; psychopathy, 2.1; psychopathy-like states, 4.8; mortality from cerebral accidents, 17.3 (including parents between 21 and 100 years of age); mortality from carcinoma, 15.

Berlit realizes the limitations of the data he presents and urges other similar surveys. As more studies such as this are collected, the conclusions will necessarily become statistically more valid. An important source of error is the difficulty of being sure of the psychiatric diagnosis. The data collected from a group of this type are somewhat more accurate than similar information from a random sample of the population.

SAVITSKY, New York.

Meninges and Blood Vessels

THE SYNDROME OF THE ANTERIOR CHOROIDAL ARTERY. T. STEEGMANN and DAVID J. ROBERTS, J. A. M. A. **104**:1695 (May 11) 1935.

Steegmann and Roberts report the case of a 17 year old boy who presented a syndrome indicating involvement of the anterior choroidal artery. The symptoms consisted of hemiplegia, hemianesthesia and hemianopia contralateral to the side of the lesion in the central nervous system. The spontaneous subarachnoid hemorrhage gave rise to the syndrome that was present shortly after the onset of the illness, as well as to the fever and signs of meningeal irritation. The pain in the right eye was probably due to the irritating effect of the blood in the subarachnoid space on the ophthalmic branch of the trigeminal nerve. Pain in the right eye followed by headache had occurred seven years previously but had not been followed by other symptoms. The question of the relationship of trauma, which occurred two and one-half months before the cerebral insult, is of doubtful significance. The clinical picture of simple occlusion of the anterior choroidal artery is variable, depending on the site of occlusion. When hemorrhage occurs, as in the authors' case, the analysis is even more complex, because of the parts that pressure, ischemia and edema play in the process. The clinical facts indicate that the maximal damage was done in the region of the lateral geniculate body and the area in which the optic radiations begin. The area of the most posterior portion of the internal capsule was involved in the process to a lesser extent. The most reasonable explanation of the clinical picture would be to assume that rupture of the anterior choroidal artery itself occurred near the anterior pole of the lateral geniculate body. The infiltration of blood into the subarachnoid space could produce an irritating effect on the ophthalmic branch of the fifth nerve and thus explain the entire clinical picture. A question that arises is whether the picture presented by the symptoms could be produced by lesions resulting from the occlusion of other cerebral vessels. The studies of Charles Foix show that hemianopia due to a lesion of the right sylvian artery is accompanied by monoplegia of the arm or hemiplegia predominating in the arm. The hemianopia is of a type found in the lower quadrant. Total occlusion of the sylvian artery is fatal in a short time. On the other hand, a lesion resulting from occlusion of the posterior cerebral artery produces hemianopia of the upper quadrant with an associated syndrome of thalamic involvement. A light form of hemiplegia with signs of cerebellar involvement may also occur, according to Poppi. The authors believe that the condition in their case fits more into the picture of the syndrome produced by involvement of the anterior choroidal artery. In cases in which no anatomic studies are possible, a better descriptive clinical term would be the geniculocapsular syndrome.

EDITOR'S ABSTRACT.

NERVOUS MANIFESTATIONS IN PATIENTS WITH ARTERITIS NODOSA OF KUSSMAUL. C. I. URECHIA and N. ELEKES, Ann. de méd. **36**:466 (Dec.) 1934.

Polyneuritis is an early symptom in cases of periarteritis nodosa. Many observers have described histopathologic changes in the form of neuropathies pro-

duced by disturbances in the vascular supply of the affected nerves. Others found no periarteritis on microscopic study and assumed that a neuropathy existed due to a "toxic" condition. Clinical manifestations in this disease indicating involvement of the central nervous system are headache early in the course of the disease and convulsive states in the later periods, the anatomic equivalents of which may be meningeal hemorrhages, cerebral anemia, and edema following renal or hepatic disease. In isolated cases, clinical examination disclosed acute leptomeningitis, with mild pleocytosis, an increase in the albumin content and changes in the colloidal gold curve of the spinal fluid. Ocular disturbances occurred, such as anisocoria, nystagmus and retinal changes, pointing to a coexistent encephalitis or nephritis. Clinical symptoms indicating encephalitis or myelitis were rarely encountered. When present, they consisted of mild intermittent fever, hemiplegia or paraplegia, symptoms referable to the extrapyramidal systems, palsy of some of the cranial nerves, ataxia and athetosis. Mental disturbances were exceptional and were observed only during the terminal periods of the disease. Histologically, in such cases of encephalitis there was a nodular or more diffuse arteritis involving all three layers of the larger arteries with a cellular infiltration of lymphocytes and plasma cells and occasionally of giant cells. This inflammation led to gradual destruction of the walls of the vessels and to the formation of thrombi, with ensuing perivascular hemorrhages and multiple foci of hemorrhagic softening. Veins were similarly affected. More or less extensive foci of destruction of myelin sheaths and axis-cylinders, of disease of the ganglion cells and of glial proliferation could easily be explained as sequelae of the widespread vascular disease.

WEIL, Chicago.

PERIPHERAL ARTERIAL SPASMS, CHRONIC RETINAL ARTERITIS AND GENERAL VASCULAR DISTURBANCES. J. GALLOIS, Ann. d'ocul. **172**:153 (Feb.) 1935.

Gallois reports the cases of several young persons who presented peripheral angiospasm. In these persons chronic retinal arteritis, commonly observed in elderly arteriosclerotic patients, was noted. In several, general vascular disturbances were also noted. In other patients a definite vascular heredity was present. Whenever chronic retinal arteritis is observed in a young person the entire circulatory system should be investigated.

BERENS, New York.

DISTURBANCES IN CEREBRAL CIRCULATION FOLLOWING ARTERIOGRAPHY. G. BODECHTEL and F. W. WICHMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:673 (Dec.) 1934.

Two patients, both of whom were suspected of having tumor, were given injections of colloidal thorium dioxide by way of the internal carotid arteries and died a few hours later. The first patient showed previous arterial disease with a superimposed sinus thrombosis. The second patient had a tumor with numerous recent hemorrhages and necrotic lesions in the bed of the tumor, the basal ganglia and the cortex of the island of Reil. Arteriography should be used only when the tumor is unlocalized. Sinus thrombosis is a contraindication for its use. Thorium dioxide should be injected only after long experience has insured its safety.

MICHAELS, Boston.

Diseases of the Brain

APHASIA IN BRAIN TUMORS. T. H. WEISENBURG, Ann. Surg. **101**:373 (Jan.) 1935.

Sixty cases of aphasia were selected for a critical analysis of this condition in relation to tumor of the brain. In fifteen cases the lesion occurred in the space-taking areas of the brain. In ten of the fifteen cases the aphasic symptoms were present before operation; in two others there were alterations in personality with

other vague symptoms, which on closer analysis might have been shown to be aphasic, while in the remaining three the disturbances of speech developed after operation. In practically all cases the aphasic symptoms were of help in localization of the lesion, and in three, because of their early appearance and the paucity of other symptomatology, the disturbances of speech were of distinct value, but only in determining the side of the brain on which the lesion was located. By no means was there any evidence of a stricter localization.

On the basis of the type of lesion, the cases of tumor as a group differed from those in which the lesion was vascular in two characteristics: The symptoms were more variable, and, with the exception of those with amnesia, the patients presented less clearcut disorders. The greater variability is undoubtedly to be related to the acute lesions and to the rapid pathologic changes. The manifestations in the cases of tumor were more difficult to classify as either predominantly expressive or predominantly receptive. The fact that the expressive and receptive disorders were more complicated in the cases of tumor than in the cases of vascular lesions was due to the larger area affected in the former. Another factor of importance was the fact that in the cases of tumor there was not complete destruction of the invaded tissue.

GRANT, Philadelphia.

MUSHROOM POISONING (MYCETISMUS): REPORT OF FOUR CASES. JOSEPH B VANDER VEER and DAVID L. FARLEY, Arch. Int. Med. **55**:773 (May) 1935.

Cases of acute mushroom poisoning are reported in four adults in whom symptoms developed several hours after the eating of cooked mushrooms of the Amanita phalloides variety. One patient was jaundiced, complained of blurred vision and failed rapidly, dying on the fifth day after ingestion of the toadstools. At autopsy the brain was edematous and congested, with scattered punctate hemorrhages under the floor of the fourth ventricle and in the midbrain. The ganglion cells in the cortex were reduced in number and showed toxic swelling. In the medulla there was a focus of glia cells. Fat was present in the cortical ganglion cells, the ependymal cells and the astrocytes, among the microglia and in the endothelium of the vessels. The second patient was jaundiced and semicomatose and sank rapidly, dying a week after the ingestion of the fungus. At autopsy the brain was edematous and congested, manifesting widespread toxic degeneration of the ganglion cells. In the cortex the vessels showed perivascular infiltration by lymphocytes. A similar invasion was noted in the vessels of the basal ganglia. Fat was found almost everywhere throughout the brain. The third patient was the first of the quartet to become sick after eating the mushrooms. She suffered from cramps, diarrhea, nausea, vomiting, jaundice and mental excitement but regained health slowly and was able to do housework within six weeks after the beginning of the attack. Her husband, who had also eaten the mushrooms, had taken 2 ounces (62.6 Gm.) of magnesium sulfate nine hours after ingestion of the toadstools. He suffered from a short period of vomiting, cramps and purgation but was out of bed within a few days and back to normal health in less than a fortnight. The cause of death was probably the toxic damage to the brain cells.

DAVIDSON, Newark, N. J.

INTRADIPLOIC EPIDERMOID (CHOLESTEATOMA) OF THE SKULL. PAUL C. BUCY, Arch. Surg. **31**:190 (Aug.) 1935.

Three cases of epidermoid tumor (cholesteatoma) arising within the diploe of the skull are reported. Such neoplasms are very rare, only thirteen having been recorded prior to the present report. These tumors, which arise from displaced anlagen of surface epithelium, expand the diploe and separate and erode the tables of the skull. There is a characteristic defect visible in the roentgenogram. These intradiploic cholesteatomas rarely give rise to neurologic symptoms. The treatment is purely surgical. A permanent cure may be expected only if the tumor is completely removed.

GRANT, Philadelphia.

CEREBRAL NEOPLASMS: DIAGNOSIS IN ABSENCE OF GENERALIZED INTRACRANIAL PRESSURE PHENOMENA. A. E. BENNETT and J. J. KEEGAN, J. A. M. A. **104**:10 (Jan. 5) 1935.

Bennett and Keegan present reports of twelve cases of cerebral tumor in which a generalized increase in intracranial pressure was absent. None of the patients presented changes in the fundus of the type due to pressure. In only two instances was the pressure of the spinal fluid above 10 mm. of mercury during the period of diagnostic observation. One patient had a pressure of 14 mm. and another a pressure of 16 mm., giving the first indication of a lesion due to pressure. Headache was noted in only two instances, and in these increased pressure was a doubtful cause. Vomiting was not present in any case during the period of diagnostic observation. The most valuable single early diagnostic symptom was focal spasms. In eight cases jacksonian seizures were present. One patient had been treated for essential epilepsy for about ten years. In five cases the earliest symptom was, respectively, a change in the sensorium, progressive blindness, progressive choreiform movements, recurrent hemiparetic attacks along with focal spasm and lethargy with diplopia. In six cases roentgen examination showed localized changes suggestive of localized pressure, with other conditions suggestive of an intracranial neoplasm. In seven cases encephalographic studies were made and considered diagnostic of tumor, with accurate localization in each instance. In four of these cases there were marked distortion, compression and displacement of the lateral ventricles, indicating large tumors, but there was no definite increase in the intracranial pressure. In two cases roentgen studies of the skull were not made. In nine cases a diagnosis of cerebral neoplasm was made in the absence of phenomena of generalized intracranial pressure. In three instances a diagnosis of inflammatory encephalopathy was considered more likely. In one case the correct diagnosis of tumor was made later in another clinic by encephalography. In one patient, an 8 year old child, the presence of a tumor was not suspected; the growth was found at necropsy. In another child a typical syndrome of epidemic encephalitis was present. At necropsy gross examination revealed what was apparently a tumor of the third ventricle, but the histologic report gave the diagnosis as encephalitis. Two tumors in the region of the third ventricle presented the greatest diagnostic difficulties in this group because of the febrile disorder, the short duration of the illness and the complete lack of pressure phenomena. There was excellent functional recovery in three cases in the group and palliative relief for several months after decompression and partial removal in three other cases. In the fatal cases, five patients with a highly malignant glioblastoma multiforme died within one year after the onset of symptoms. In two cases oligodendroglioma recurred and death occurred within two years. One patient is still alive and in good health three years later. One patient with a craniopharyngioma died within ten months. Two of the three patients who recovered had benign meningiomas.

EDITOR'S ABSTRACT.

WATER INTOXICATION: REPORT OF FATAL HUMAN CASE, WITH CLINICAL, PATHOLOGIC AND EXPERIMENTAL STUDIES. FERDINAND C. HELWIG, CARL B. SCHUTZ and E. CURRY, J. A. M. A. **104**:1569 (May 4) 1935.

Helwig, Schutz and Curry report a case in which death apparently resulted from water intoxication, the patient absorbing 9,000 cc. of tap water by proctoclysis. They have been able to produce identical symptoms and pathologic changes in seven consecutive rabbits by the administration of large amounts of tap water rectally. In their experimental studies the carbon dioxide-combining power of the blood plasma was never increased and was usually decreased. The gross and microscopic studies of the brains both of the patient and of the experimental animals seem strongly to support the hypothesis advanced by Rowntree. Explanation of the exact mechanism of water intoxication presents many interesting and complicated problems. It is difficult to account for the apparent susceptibility

of the liver and brain for retaining fluid when tap water is given intestinally. It would appear that water intoxication is dependent on water elimination. The reason the kidneys fail to eliminate properly is unknown. The studies of Meier and Mann seem to indicate that some hepatic dysfunction may be of importance in the pathogenesis of water intoxication. Biopsy of the liver of the authors' patient at the time of operation showed a very advanced parenchymatous degeneration. Moreover, in the livers of all their experimental animals varying degrees of cloudy swelling were uniformly present. It has been impossible to produce an intoxication when hypotonic salt solution was administered or when a 10 per cent solution of sodium chloride was given prior to the administration of water. One may speculate as to whether an upset in the normal salt-water balance produces water intoxication or whether a lack of chlorides interferes in some way with the apparent relationship of the liver to the renal output. The mechanism of the acute cerebral edema is puzzling. The most striking characteristic of the edema was its interstitial character and the fact that at necropsy there was no evidence of increased production of cerebrospinal fluid. The ventricles were decreased in caliber, and there was scarcely any cerebrospinal fluid present, while apparently paradoxically, there was histologic evidence of definite hyperactivity of the choroid plexus. Terplan attributes the cerebral edema to a hypotonic condition of the blood due to a marked diminution in the blood sugar. Perhaps the most important factor in the production of the cerebral edema, which is the major pathologic lesion of water intoxication, is a disturbance in the normal isotonicity of the blood.

EDITOR'S ABSTRACT.

ENCEPHALO-MYELITIS DISSEMINATA FOLLOWING ASCENDING NEURITIS. ROSS H. THOMPSON, J. Nerv. & Ment. Dis. **81**:373 (April) 1935.

Thompson presents in detail the case of a young man who complained of pain and later of numbness of the region of the left deltoid muscle two weeks after the subsidence of a severe infection of the hand. Later there developed extension of the numbness over the entire upper extremity, the trunk and lower extremity of the same side. There were marked clumsiness of movement in the upper extremity, spontaneous nystagmus and atrophy of the muscles of the upper limb and shoulder girdle, with diminished muscular power. There was complete astereognosis in the left hand. The author reviews the literature on the route of infections entering the subarachnoid space in cases of neuritis. There is abundant evidence in favor of a direct communication between the lymph spaces in the perineural sheaths of the spinal nerves and the spinal subarachnoid space. Ascending neuritis may thus be an avenue of distribution of peripheral infection to the spinal cord and brain.

HART, Greenwich, Conn.

JUVENILE PARETIC NEUROSYPHILIS STUDIES: III. DEVELOPMENTAL HISTORY. WILLIAM C. MENNINGER, J. Nerv. & Ment. Dis. **81**:389 (May) 1935.

This paper is a continuation of Menninger's studies on juvenile dementia paralytica and is concerned with the mental and physical development of the patient and with psychic trauma, physical trauma and the frequency of convulsions. Forty per cent of 426 patients with juvenile dementia paralytica were fundamentally retarded in mental development. In 60 per cent the mental development was normal until the onset of the disease. A brief report is made of 67 cases of hypophrenia, congenital syphilis being the etiologic factor in 29.8 per cent. Menninger declares that hypophrenia in cases of juvenile dementia paralytica is in no way different from other forms of mental deficiency but concludes that it is incorrect to assume that juvenile dementia paralytica develops in feebleminded persons. Psychic trauma was reported as a precipitating factor in 18 of 653 cases. Normal physical development occurred in 50 per cent of 349 cases. In 35 per cent there was retarded

development which results in a kind of infantilism, though rarely of the Lorain type. It is primarily an arrest of growth with a stunted development and consequently a poorly proportioned body. Physical trauma is recorded in 35 of the 349 cases and is regarded merely as a precipitating factor. Convulsions were recorded in the history in 111 cases, or 31.8 per cent of cases in which adequate data were available. Convulsive seizures occurring prior to other symptoms and signs of juvenile dementia paralytica may be typical of and indistinguishable from the convulsions occurring in cases of idiopathic epilepsy.

HART, Greenwich, Conn.

PERSISTENT HEADACHE DURING LACTATION. JULIUS H. BEILBY, Brit. M. J. **2:** 337 (Aug. 24) 1935.

A persistent headache for which no underlying cause is discoverable and which disappears on weaning may be associated with lactation. The condition is uncommon but has been found by Beilby in five multiparas. It is usually present in the frontal region but may affect the entire head. The intensity of the pain varies. No pathologic basis for the complaint was traceable. The urine, blood pressure and the eyegrounds were normal before, during and after parturition. It occurs chiefly among women in poor circumstances or of poor physical status, for whom nursing is an added burden. Treatment must be directed toward improving the general condition of the patient during the prenatal and puerperal periods. If this fails, weaning, which is curative, becomes necessary.

BECK, Buffalo.

CONTRIBUTION TO THE STUDY OF THE PATHOGENIC RÔLE OF DISTURBANCES OF THE ENDOCRINE SYSTEM IN EPILEPSY. J. S. RABINOVITCH, Encéphale **30**:250, 1935.

In a group of 300 epileptic patients, 14 (2 men and 12 women) suffered from clinically apparent disturbances of the endocrine system, renal diabetes, hirsutism with an arrest of growth following precocious maturity in the men and simple goiter, exophthalmic goiter, hyperthyroidism with periodic amenorrhea, mild obesity of the pituitary type, precocious menopause, periodic amenorrhea, oligomenorrhea, preclimacteric disturbances and tetany in the women. The function of the endocrine glands was studied in these cases as well as in 20 others in which there were no clinical manifestations of endocrinopathy. In 12 of 17 women the convulsions had a definite relation to the menstrual function. In 5, the attacks occurred mostly or entirely during or immediately preceding menstruation. In 2 women with occasional amenorrhea the attacks coincided with the periods or, if the periods were absent, with the date on which they were to have occurred. In 2 others attacks took place only when menstruation was absent. Two patients were beginning to undergo premature menopause, and 1 was in the preclimacteric period. Of 29 women studied, the sugar content of the blood was normal in 12, low in 11 and high in 6. The cholesterol content was markedly low, values of from 70 to 90 mg. per hundred cubic centimeters being the rule. The basal metabolic rate was normal, except in 2 cases, in which it was + 27 per cent and — 21 per cent, respectively. The amount of calcium varied between 10.6 and 12.6 mg. per hundred cubic centimeters, except in 1 case of tetany, in which it was 8 mg. The amount of potassium in the blood varied from 17.7 to 20.2 mg. per hundred cubic centimeters. The potassium-calcium ratio averaged 1 : 6. The nonprotein nitrogen level was always normal. The alkali reserve was slightly lowered in 1 case. The sedimentation rate was diminished in most cases; with a few exceptions it varied from 2 to 3.5 mm. in one hour. The leukocyte picture was generally normal. In the cases of endocrinopathy the lymphocyte count varied from 35 to 50 per cent.

LIBER, New York.

PATHOGENIC RÔLE OF ENDOCRINE DISTURBANCES IN EPILEPSY. J. S. RABINOVITCH, Encéphale **30**:350, 1935.

In a clinical and biochemical study of thirty-four epileptic patients Rabinovitch observed that epileptic seizures occur particularly during menstruation and in persons with amenorrhea often at the date of the expected period. The blood sugar curve during fasting is polymorphous and labile. The blood sugar content often drops to 40 mg. per hundred cubic centimeters or even lower two hours after the ingestion of dextrose. Hypoglycemic curves occur in cases of all types of epilepsy but more particularly in cases of petit mal and psychic equivalents and in those in which the patient presents the heredofamilial history described by Bratz: left-handedness, stammering, enuresis and epilepsy. The hypoglycemic phase alone is, however, insufficient to provoke an attack. The basal metabolic rate is generally normal. Its variations are not correlated with the frequency or intensity of the epileptic seizures. In one epileptic patient suffering from exophthalmic goiter, thyroidectomy was followed by a lowering of the basal metabolism without any change in the rhythm of the attacks. In most cases a slight lowering of the alkali reserve and slight hypercalcemia were found.

In general, the endocrine and vegetative systems are very unstable, although epilepsy is not as a rule associated with any frank endocrinopathy. No endocrine condition can result in epilepsy without concomitant lesions of the nervous system. According to Buscaino's expression, in all epilepsy there are a cerebropathy and a biopathy. In view of the researches of Frisch and others showing that retention of water is a factor in the production of the seizure, Rabinovitch believes that endocrine and vegetative disturbances exert their influence by producing retention of water. He rejects the classic concept that the sympathetic nervous system and the glands innervated by it are epileptogenous, while the vagus nerve and the glands innervated by it are antiepileptic. A notable incongruity of this schema is the necessary inclusion in the vagus group of the pancreas, the excessive functioning of which is known to be epileptogenous. From the water retention hypothesis, Rabinovitch derives the following schema:

Glands which oppose epileptic manifestations	Glands which favor epileptic manifestations
1. Adrenals	1. The Langerhans apparatus of the pancreas
2. Thyroid	2. Posterior lobe of the hypophysis
3. Parathyroids	3. Persistent thymus
4. Anterior lobe of hypophysis	4. Epiphysis (?)
5. Genital glands	5. Corpus luteum (??)

LIBER, New York.

EPILEPSY PRODUCED BY SKIN PARASITES (A NEW FORM OF EXPERIMENTAL EPILEPSY). P. PAGNIEZ, A. PLICHET and R. LAPLANE, Presse méd. **41**: 1557 (Oct. 6) 1934.

Brown-Séquard produced a form of typical grand mal epilepsy in the guinea-pig by partial section of the sciatic nerve. He noted two phenomena resulting from the operation: (1) analgesia of the corresponding side of the head and neck and (2) convulsive attacks induced by pinching this zone. He therefore designated this region as an epileptogenic zone. He attributed the epilepsy to the lesion of the sciatic nerve. The authors found that the real etiologic agent of the epilepsy was a multiplication of lice in this zone. These lice were mallophages of the species Gyropus ovalis. Suppression of the lice by chemical (xylene, mercury bichloride, 2:100 and hydrous wool fat by inunction) or mechanical means led to the disappearance of the convulsions. The lice act as reflex irritants. Other parasitic infections, such as the helminthes, are sometimes associated with convulsive phenomena, and research along these lines may throw further light on the nature of epilepsy.

N. MALAMUD, Ann Arbor, Mich.

THE IMPORTANCE OF THE SIGN OF VESTIBULAR DISHARMONY IN A CASE OF ABSCESS OF THE CEREBELLUM. L. LEVESQUE, F. BARRON and A. CHARBONNEL, Rev. d'oto-neuro-opht. **13**:186 (March) 1935.

The case reported was that of a child, aged 5 years, who during convalescence from bilateral mastoidectomy after an attack of scarlatina, suddenly experienced fever, occipital headache and hyperextension of the neck. Associated with it was a disharmonious vestibular syndrome, consisting of nystagmus to the diseased side, deviation of the arms, Romberg's sign and lateropulsion in the same direction as the nystagmus; there was a slight but distinct cerebellar dysmetria, which of itself was not sufficient evidence on which to base a diagnosis of abscess of the cerebellum. On account of these two syndromes immediate exploration of the cerebellum was made, and an abscess was evacuated. Later, the deviation of the arms and the Romberg sign were changed in direction. Death occurred suddenly two months after intervention from an undetermined cause. The association of the disharmonious vestibular syndrome was the deciding factor in the diagnosis.

DENNIS, Colorado Springs, Colo.

A STUDY OF HUNTINGTON'S CHOREA IN A FAMILY GROUP. K. WASUM, Arch. f. Psychiat. **103**:78 (Feb.) 1935.

Wasum studied cases of Huntington's chorea in which he was able to determine the presence of this disease in five generations. Seventy-six members of the family were included in this study. The chorea was of the pure Huntington type. It was found that the chorea was transmitted in a direct line, so that the descendants of persons who did not have chorea were free from the disease. There was a tendency for anteposition of the onset of the disease so that from generation to generation the onset occurred at a progressively earlier age. In all the patients the disease began with psychic disturbances, such as outbursts of anger, jealousy and irritability. Following these there developed the first signs of motor disturbances, which seemed to cease during sleep in all the patients; finally there was development of deterioration. Neurologically, the symptoms were primarily of the extrapyramidal type. Anatomically, there were gross atrophies of the basal ganglia. The histologic picture was characterized by destruction of ganglion cells and proliferation of astrocytes and fibrous glia, with marked atrophy of the nerve fibers. These findings were particularly pronounced in the striatum.

MALAMUD, Iowa City.

THE SIGNIFICANCE OF POLYOPIA IN THE DIAGNOSIS OF TUMOR OF THE OCCIPITAL LOBE. H. HOFF and O. PÖTZL, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**: 433 (March) 1935.

Hoff and Pötzl present the case of a man aged 49 who was seen because of a convulsion. He was well for two weeks, and then there developed monocular diplopia with either eye, the false image being to the left. After two more convulsions polyopia set in, with multiple false images to the left. The patient then complained of difficulty in seeing on the left side. The convulsions continued and were preceded by uncinate phenomena and visual hallucinations. Later, there were found left homonymous hemianopia, hyperactivity of the tendon reflexes in the left upper extremity and a tendency to fall to the left with the eyes closed. There was bilateral papilledema. The differential diagnosis lay between a tumor of the temporal lobe and a tumor of the occipital lobe. The hemianopia, the uncinate aura, the changes in the tendon reflexes and the results of the labyrinthine tests were not decisive. The only valuable guide to localization was the polyopia which preceded the hemianopia. This pointed clinically to a condition of the occipital convexity near the pole. The distribution of the polyopic images in the horizontal meridian suggested the probability that the main lesion was in the middle of the polar end of the area striata in the region of the second occipital gyrus. The presence of convulsions indicated the probable proximity of the lesion

to the cortex. The epileptic convulsions, the deviation of the head and eyes and the uncinate phenomena pointed to probable extension of the lesion anteriorly.

At an operation the right occipital and right inferior temporal regions were exposed. An intracerebral tumor was found in the parieto-occipital region. No tumor was present in the temporal lobe. The tumor was a glioma; it lay in the occipital pole and extended into the lingual and the fusiform gyri. The calcarine area was free, but its lingual lip was pushed upward by the tumor. The occipital cortex was compressed but not infiltrated by the tumor. The polar end of the area striata was compressed.

The visual hallucinations were probably due to compression of the occipital cortex. The polyopia was a result of the stretching of the cortex in its polar extremity. The hemianopia was due to infiltration of the optic radiations near the inferior horn. As this field defect came late in the course of the disease, the tumor probably grew postero-anteriorly. The authors note the presence of uncinate auras in spite of the intactness of the cornu Ammonis and the limbic area.

The purpose of this communication is essentially to emphasize the diagnostic value of polyopia. The authors have discussed in other publications the pathologic physiology of this interesting symptom. They believe that polyopia is the result of two conflicting tendencies: Attempts to fixate the object and forced conjugate deviation of the eyes. Fixation is faulty due to the condition of the occipital pole, and the impulse to deviate is due to irritation of the occipital cortex.

SAVITSKY, New York.

Diseases of the Spinal Cord

THE RELATION BETWEEN CHRONIC ANTERIOR POLIOMYELITIS OR PROGRESSIVE SPINAL MUSCULAR ATROPHY AND AN ANTECEDENT ATTACK OF ACUTE ANTERIOR POLIOMYELITIS. LEON A. SALMON and HENRY ALSOP RILEY, Bull. Neurol. Inst. New York **4**:35, 1935.

Salmon and Riley state that no serious consideration of the possibility of a relationship between a chronically progressive disease affecting the muscular system and a former attack of acute anterior poliomyelitis is found in the standard textbooks of neurology in the English language, although this relationship is recognized by some foreign authors. During the course of the last half century a number of authors have observed the occurrence of various types of neurologic involvement after an attack of acute anterior poliomyelitis in childhood or in early adult life. The total number of recorded cases is fifty-nine. Among these the principal disorders attributed more or less directly to an antecedent attack of acute anterior poliomyelitis or progressive spinal muscular atrophy are, subacute myelitis in the form of a diffuse spinal involvement, six cases; congestive phenomena with transitory paresis or paralysis, two cases, and acute myelitis (Brown-Sequard syndrome), two cases.

Three cases are reported in which unquestionable evidence of chronic anterior poliomyelitis or progressive spinal muscular atrophy was present many years after an attack of acute infantile paralysis. Case 1 was that of a man, aged 64, who had had an attack of anterior poliomyelitis at the age of 5. The onset of the secondary disorder began at the age of 59. The course was typical of chronic progressive poliomyelitis. Case 2 was that of a man, aged 30, who had had an attack of anterior poliomyelitis at the age of 6. At the age of 15 some wasting and progressive weakness in the muscles of the thenar eminence of the left hand were observed. At the age of 19 a symmetrical atrophy of the muscles of the right thumb appeared, and in 1933 further extension of progressive atrophy of the muscles of the hand was noted. The chronic process was widespread. Case 3 was that of a man, aged 31, who had suffered from anterior poliomyelitis at 2½ years of age, which left him with weakness of the right foot. At 18 there were noted increasing weakness of the right lower extremity and wasting of muscles of the calf. For the two years prior to his admission to the hospital the left leg also felt heavy.

KUBITSCHEK, St. Louis.

TWO CASES OF ECCHONDROSIS OF THE LUMBAR REGION WITH ANGIOSPASM OF THE FOOT: COMPLETE RECOVERY AFTER OPERATION. L. PUUSEPP, Bull. et mém. Soc. nat. de chir. **61**:24 (Jan. 19) 1935.

Elsberg described a form of extradural ventral chondroma which was not neoplastic but was due to hypertrophy of the intervertebral disks. This he designated as ecchondrosis. The cartilaginous overdevelopment gradually exerts pressure on the cord and leads to myelitis. When the lumbar region is thus affected, compression of the cauda equina and symptoms of sciatica result. The author reports two such cases which, in addition to the neurologic symptoms, showed signs of angiospasm of the corresponding foot. This he interprets as a vasoconstrictor reflex determined by the painful irritation of some of the roots of the cauda equina, the reflex being transmitted by branches of the sympathetic system. Surgical measures in such cases lead to recovery.

N. MALAMUD, Ann Arbor, Mich.

PATHOGENESIS OF SYRINGOMYELIA: CLINICOPATHOLOGIC STUDY OF ONE CASE. R. BURDETT and F. E. POSTUMUS MEYJES, Encéphale **30**:137, 1935.

In a child aged 6 years atypical symptoms had been diagnosed as psychoneurotic by several pediatricians. Examination showed paresis of both upper limbs, ankle clonus and rigidity of the neck. The roentgen findings were normal. Examination of the spinal fluid showed a positive reaction to the Nonne-Apelt test, 20 lymphocytes, no micro-organisms and a negative Wassermann reaction. Iodized poppy-seed oil 40 per cent was arrested at the level of the first thoracic vertebra. The child died of acute bronchopneumonia before an operation could be performed. Autopsy showed two intraspinal tumors at the level of the fourth cervical vertebra, histologically resembling medulloblastoma. Between these tumors a column of glial tissue occupied the dorsal funiculus. It contained a syringomyelic cavity, distinct from the central canal, surrounded by small round glia nuclei, elongated nuclei of connective tissue type, abundant mesenchymatous fibers and iron pigment. A diffuse inflammatory process, consisting of lymphoplasmocyte perivascular muffs, was most marked in the ventral horns and at the limits of the pathologic tissue. The dorsal vagus nuclei were atrophied and "flattened" by distention of the fourth ventricle, which explained the absence of a reflex cough during the bronchopneumonia and the persistence of the voluntary cough.

LIBER, New York.

Vegetative and Endocrine Systems

ANTERIOR PITUITARY AND ANTERIOR PITUITARY-LIKE SUBSTANCES: THERAPEUTIC APPLICATIONS. EMIL NOVAK, J. A. M. A. **104**:998 (March 23) 1935.

Novak states that the employment of the growth hormone preparations is indicated in cases of the various conditions due to deficiency of the pituitary gland. The results are usually not striking and will probably not be improved on until biochemists isolate the hormone and produce more potent preparations. The anterior pituitary-like preparations are probably of no value when used alone in the treatment of amenorrhea, and even when combined with estrogenic substance the results are very little improved. The anterior pituitary-like preparations made from the urine of pregnant women have appeared to give excellent results in many, though not by any means all, cases of functional uterine bleeding, so that when this disorder is encountered in young women, for whom roentgen therapy is undesirable, the method should certainly be tried. The comparatively small group of cases thus far reported in which undescended testicle has been successfully treated by the anterior pituitary-like preparations make this method seem promising and worthy of more extended trial, especially as the surgical treatment of this condition is not as satisfactory as might be wished. There is no objection to a trial of the anterior pituitary-like preparations in the occasional mysterious and baffling cases of habitual abortion, although the results are not much more clearly defined than

is the etiology of the condition. These preparations appear rational as adjuvants in the treatment of primary dysmenorrhea, although correction of constitutional and psychic factors is often much more important and should never be overlooked. As to other conditions, such as aspermia and baldness, the clinical data thus far available are much too meager for one to draw conclusions as to the results of treatment with the anterior pituitary-like preparations, and there are physiologic reasons to make one question the value of this plan. It is possible that the results of organotherapy in various conditions produced by deficiency in the activity of the anterior lobe of the pituitary gland may be improved with preparations of the gonad-stimulating hormones obtained from the anterior lobe itself.

EDITOR'S ABSTRACT.

THE TESTIS HORMONE. C. R. MOORE, J. A. M. A. **104**:1405 (April 20) 1935.

Moore discusses the biologic functions of utility that the testicle exercises in the organism. He presents some of the general phases and particular details of the testis hormone (androgenic hormone) and discusses some of the principles and possibilities of its clinical application. The experimental animal must be depended on for presenting the various aspects, since knowledge of the manifestations of hormonal deficiencies in man, of methods of detecting the presence or absence of the hormone or of its utility in the species is so limited as to be of little value. It is apparent that the question of the clinical value of androgenic substance is by no means settled. For attaining dependable results the problem must be considered from the broad point of view of social background and biologic principles. Real advancement must rest on honest critical work rather than on poorly conceived sporadic experimentation with hastily assumed results and unsubstantial claims. The principal sources of androgenic substance are the testicles of large mammals and human urine. Androgenic substance is obtained from the lipoid fraction and has been sufficiently purified to yield crystals having a high potency. It appears chemically to be a ketone alcohol; the only known method of detecting its presence consists in reactions produced in suitable animals. It is secreted continuously, or periodically, in different animals, and secretion is largely under the control of the pituitary gland. It is uncertain whether more than one hormone is secreted by the testis. Its clinical use is questionable; its primary function is the control of the accessory reproductive organs; it is not a testicular stimulant.

EDITOR'S ABSTRACT.

Cerebrospinal Fluid

CISTERNAL PUNCTURE IN SYPHILIS. J. BELGRADE and C. WRIGHT, Am. J. Syph. & Neurol. **19**:344 (July) 1935.

In cisternal puncture the physician has a method of obtaining cerebrospinal fluid which robs the spinal tap of its terrors. The prostrating headache which usually follows lumbar puncture does not develop after cisternal tap. Patients remain ambulant, going home an hour after the procedure. Except for occasional stiffness of the neck, which lasts only a few hours, no unpleasant sequelae have been reported. In an analysis of 550 consecutive cisternal punctures Belgrade and Wright report that no fatalities occurred.

The Eskuchen (indirect) method is preferred to the Ayer (direct) method. In the latter, the needle is introduced just above the spine of the axis along a line passing through the upper edge of external auditory meatus and glabella. Inserted in this plane, the needle pierces the atlanto-occipital membrane directly, without passing through bone. In the indirect technic, the advancing needle first strikes the posterior occipital protuberance, called the "point of orientation"; the handle of the needle is then raised, the needle is slightly withdrawn, the stylet is removed and a cautious advance is made. The merit of the upright position lies in the simplicity of orientation, while the advantage of keeping the patient in the recum-

bent position lies in the fact that the fluid flows spontaneously as soon as the arachnoid is reached. With the patient in the sitting posture, the pressure within the cistern is negative. If this posture is used, a mechanical compression bandage should be applied to the neck to raise the intracranial pressure. The authors state that the consensus favors the horizontal position. In performing this manipulation, a special cisternal needle with a guard should be used. Usually 10 cc. of fluid is all that need be removed, although much larger quantities may be withdrawn safely for purposes of drainage.

Contraindications to cisternal puncture are few. Increased intracranial pressure forces the brain stem into the foramen magnum, reducing or obliterating the cisterna. For this reason, retinoscopy is always a desirable safeguard in doubtful cases. Choked disk is a contraindication to the operation. Cisternal puncture should not be attempted in very young or in very old persons.

DAVIDSON, Newark, N. J.

THE CEREBROSPINAL FLUID OBTAINED BY LUMBAR AND BY VENTRICULAR PUNCTURE IN TUMORS OF THE BRAIN. CLARENCE C. HARE, Bull. Neurol. Inst. New York **4**:64, 1935.

Hare reports the results of the examination of the cerebrospinal fluid in 218 verified cases of tumor of the brain. In 186 cases the fluid was obtained by lumbar puncture and in 79 cases, by ventricular puncture. Study of the fluid was found to be of little value in the differential diagnosis of tumor of the brain from other diseases of the brain. It was found that an increase in the amount of protein and globulin in the lumbar fluid occurred in 61 per cent of cases of meningioma, in 64.8 per cent of cases of glioblastoma multiforme and in 100 per cent of cases of acoustic neuroma and of other tumors in the lateral recess of the posterior cranial fossa. It was increased in 35 per cent of cases of supratentorial astrocytoma, in 60 per cent of cases of supratentorial medulloblastoma and in 20 per cent of cases of subtentorial medulloblastoma. In cases of other pathologic types of intracranial tumor an increase in the protein and globulin contents occurred in some instances but not in others. An increase in the amount of protein and globulin in fluid removed by spinal puncture is greater than in that removed by ventricular puncture in cases of supratentorial growth. The fluid removed from the lateral ventricle on the same side as the tumor often contains more protein and globulin than that from the other ventricle. The increase of protein in the lumbar fluid varied between 50 and 490 mg., and of globulin, between 1 plus and 4 plus.

KUBITSCHEK, St. Louis.

REPEATED LUMBAR PUNCTURES OF SPINAL DRAINAGE: DIAGNOSTIC AND THERAPEUTIC VALUE IN TRAUMATIC AND ALLIED LESIONS OF CENTRAL NERVOUS SYSTEM. W. SHARPE, J. A. M. A. **104**:959 (March 23) 1935.

Sharpe states that lumbar puncture is an important diagnostic aid and that repeated lumbar punctures with drainage of the spinal fluid are of therapeutic value in selected cases of traumatic and allied lesions of the central nervous system. Diagnostic and therapeutic lumbar punctures are without danger when properly performed. The manometric attachment should always be used, and only the amount of cerebrospinal fluid necessary to lower the pressure to one half of the initial pressure should be withdrawn. In the most frequent subarachnoid type of traumatic intracranial and spinal hemorrhage in adults, children and the newborn, and in the spontaneous subarachnoid "apoplexies" in elderly persons, repeated lumbar punctures with drainage of the spinal fluid not only reduced the mortality but gave a higher percentage of recovery of function. Therapeutic lumbar punctures, combined with dehydration, have lessened the advisability of operative cranial drainage in cases of injuries to the head by about 20 per cent in adults and by more than 50 per cent in the new-born. EDITOR'S ABSTRACT.

PHOSPHORUS CONTENT OF NORMAL AND PATHOLOGIC CEREBROSPINAL FLUID. DELMAS-MARSALET and R. BARGUES, Ann. méd.-psychol. **93**:197, 1935.

The cerebrospinal fluid of normal subjects and of psychiatric patients was found to contain from 30 to 45 mg. of phosphorus per liter, the variations in amount being independent of the clinical picture. MOORE, Boston.

Experimental Pathology

EXPERIMENTALLY INCREASED INTRACRANIAL PRESSURE. WILFRED BRODGEN, FRED A. METTLER and ELMER CULLER, Arch. Otolaryng. **21**:464 (April) 1935.

Two animals were trained to respond to sound by flexing the right foreleg. As the response ceased when the animal no longer heard the tone, it was possible to determine the acuity of hearing. The threshold of hearing was determined, and the intracranial pressure was raised. The results indicate that auditory acuity is only slightly impaired, even by a marked increase of intracranial pressure. Relatively complex cortical activity is apparently possible with high degrees of intracranial pressure. The chief effect of increased intracranial pressure is produced not by pressure on the nerve tissue but by cerebral anemia caused by vasomotor failure. In cases in which there is impairment of auditory acuity with increased intracranial pressure, definite involvement of the auditory pathways by direct pressure from a tumor is to be suspected. HUNTER, Philadelphia.

LESIONS OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS PRODUCED IN YOUNG RABBITS BY VITAMIN A DEFICIENCY AND A HIGH CEREAL INTAKE. EDWARD MELLANBY, Brain **58**:141, 1935.

Most of the previously published experimental work on vitamin A deficiency and a high cereal intake was done on dogs. In the present investigation the author used rabbits, feeding them a diet containing bran, oats and calcium carbonate. Dried alfalfa in which the carotene content had been destroyed was also added. Lesions of the nervous system do not appear if alfalfa is fed in which the carotene content is not destroyed. The less the carotene content, the more intense and rapid is development of the lesion. Ergot was also given at first, but it was decided that most, if not all, of the specific lesions of the nervous system could be readily produced without giving ergot or derivatives of ergot. Control animals were maintained in a healthy state by adding the protective factor to the same basal diet as that given to the affected animals.

Young rabbits grow and remain well on the basal diet for some months. Slight stiffness of the legs, xerophthalmia and characteristic movements of the head, as if the animal did not know its position in relation to the rest of its body, develop in the order named. There is no definite paralysis, but the animals appear heavier on their legs and show fewer spontaneous movements.

Histologic studies were made of the spinal cord, brain stem and peripheral nerves. In the spinal cord degeneration was found in the following ascending paths: the dorsal columns and the dorsospinocerebellar, ventrospinocerebellar, lateral spinoreticulothalamic, spinotectal and ventral spinoreticular thalamic tracts and possibly the spino-olivary tract. Of the descending tracts, degenerated fibers were found in the rubrospinal, vestibulospinal and dorsal longitudinal bundles. The main descending tract, the crossed pyramidal tract, occasionally contained a few degenerated fibers. In the brain stem, in addition to the degeneration in the upward continuation of the ascending tracts of the spinal cord, degeneration was also found in the mesial and lateral fillets and in the ascending fibers of the dorsal longitudinal bundle. Degenerated fibers were also found in the intramedullary portions of some of the sensory cranial nerves, especially the eighth and the fifth. Generally speaking, it is the afferent side of the nervous system which is specially affected, but so far degenerative changes have been found only in the first and second neurons. All the afferent nerves of the head that were examined, the

optic nerve, the sensory fibers of the trigeminal nerve and the auditory and vestibular fibers of the acoustic nerve suffer greatly. The motor cranial nerves usually escape, but some degeneration has occasionally been found in the oculomotor nerve. In the body the same rule holds, the degeneration affecting primarily the dorsal root fibers, the anterior roots remaining normal except when the nutritional deficiency has been very prolonged. No degeneration has been seen in the vagus nerve, even in its afferent fibers.

Mellanby investigated the changes in the nerve cells in these animals. He employs the phraseology introduced by Marinesco, i. e., primary degenerative changes as the result of toxic agents and secondary degenerations due to injury of the axon. When the lesions are primary, chromatolysis commences at the periphery of the cell and spreads toward the center, whereas in secondary or traumatic degeneration the chromatolysis begins centrally and spreads toward the periphery. In the present investigation the changes in the nerve cells can be classified among the primary or toxic group, though produced by ordinary foodstuffs without the addition of any known toxic agent. On the whole, Marinesco's generalization as to the peripheral changes in the Nissl bodies in primary degeneration applies to the present results, with some exceptions. Real chromatolysis in the sense used by Nissl is not very common and when present generally affects a small portion of the periphery of the cell or the nucleus. A few instances of chromatolysis comparable with that seen in secondary degeneration were found, more especially in certain cells of the medulla. More often the granules lose their discrete form and are in a powdery or lightly staining condition, the parapyknomorphic change of Nissl. At times the Nissl bodies may be aggregated into clumps, and in other cases they may be so changed that the cell takes on a more intense, even stain and is described as chromophilic.

SALL, Philadelphia.

EXPERIMENTAL INVESTIGATIONS OF THE EFFECT OF DERIVATIVES OF BARBITURIC ACID. L. VAN DER HOST, Arch. f. Psychiat. **102**:682 (Dec.) 1934.

The derivatives of barbituric acid (especially somnifaine, soluble barbital and others) have always been known to exert toxic influences on the thalamus, cerebellum and striatum if given in large doses. Clinically, the toxic symptoms consist of incoordination and other symptoms referable to the extrapyramidal system. Pathologically, it has been found that the picture is characterized by albuminoid degeneration of the cell substance of the ganglion cells, the occurrence of metachromatic bodies in the glia and an increase in the glia cells.

Van der Host investigated this condition in five cats, some of which died following the administration for a considerable time of high doses of somnifen; others also showed symptoms of intoxication and were afterwards subjected to histologic examination. The clinical symptoms during the process of intoxication were referable to the extrapyramidal system. Pathologically, the changes were found particularly in the respiratory center, in the vagus nucleus and in the cerebellum, especially the dentatum. The thalamus was not affected, but there were found severe lesions in Deiter's nucleus and in the other vestibular nuclei. Histologically, these changes were similar to those already described, that is, degeneration in the ganglion cells, the occurrence of metachromatic products in the glia and glial proliferation.

MALAMUD, Iowa City.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Oct. 17, 1935

C. A. McDonald, M.D., *Presiding*

Suicide Among Civilized and Primitive People. Dr. Gregory Zilboorg.

It is customary to consider suicide as a pathologic phenomenon due to more or less severe disturbances in the normal functions of the psyche and to seek for the causes of suicide either in the constitutional psychopathic characteristics of man or in severe environmental conditions created by civilization. Even the unsatisfactory statistical data at hand cast serious doubt on the validity of the traditional views on suicide. A study of suicide among primitive races suggests that: (1) suicide is a universal phenomenon and mental disease is by no means a prerequisite of its incidence; (2) all methods and motivations of suicide met among civilized men are found among persons of primitive races who commit suicide.

The following hypothesis appears to be warranted and further study is invited: Suicide originated in passive murder (voluntary human sacrifice of slaves and women at the grave of a dead chief). This passive murder—a form of primitive mourning acted out in dramatic form—gradually evolved into more frank suicidal attempts, various forms of which are found among civilized people today. As to methods of self-destruction, it appears that strangulation, the prototype of hanging, is probably the most ancient.

The various characteristics of the psychologic state associated with suicide as one finds them in patients are not easily or at all understood unless the psychologic attitude found in primitive people toward suicide is taken into account. The careful investigation of this psychologic attitude among primitive races sheds a definite light on the psychogenesis and pathogenesis of suicide as it occurs today.

Clinical examples were paralleled with illustrations of corresponding reactions among primitive races.

DISCUSSION

Dr. A. W. Stearns: I have been particularly gratified with this paper, as a number of years ago my interest in the problem reached the saturation point, and I have been somewhat dismayed at the relatively small amount of attention which a subject of so much importance has received from psychiatrists. To this day there are available few studies of cases. It is not my purpose to dispute Dr. Zilboorg, nor could I do so honestly, as in the main his observations arouse in me a sympathetic response. I wish merely to emphasize some doubts which he has expressed by inserting an occasional question.

I think all can agree as to the damaging effect of prejudice in warping scientific judgment. One may confess that when emotion is aroused it tends to take the right of way, ruthlessly pushing aside rational effort. Intelligence often appears a mechanism with which feeling carries out its dictates. It seems true that a person who commits suicide is neither a hero nor a coward but one who has expressed feeling in the superlative.

I wish to raise a question as to the validity of the concept of the instinct for self-preservation. It will be recalled that McDougall, in one of his later books, abandoned the word instinct in favor of the term propensity. While he said that he had not changed his mind, the use of the word instinct involved him in so much trouble that he felt safer with the word propensity.

It is true that there are a number of propensities the expression of which results in self-preservation. An infant on falling into the water struggles violently. The biologic purpose of the struggle may be self-preservation, but it seems more

likely that the infant is merely reacting to a series of unpleasant stimuli. In panics human beings struggle ferociously, often to their own injury. Biologically they may be trying to preserve themselves, but practically they are reacting to fear. Social custom frequently elevates one's necessities by establishing ethical and moral codes. In this way, what is natural often appears to be the result of social evolution. It is interesting to know that there is a copy of John Donne's book in the Harvard College Library, one of the few which have survived.

There seems to be an ebb and flow in the attitude of society toward suicide. It was permitted by Roman law and was supposedly rather common. The attitude of the church in legislating against it seems to have been a procedure of social defense. The large number who sought martyrdom has been held responsible for this.

Dr. Zilboorg believes that he has satisfactorily disposed of the time-honored belief so ably set forth by Morselli that the rate of suicide increases with the development of civilization. This requires discussion. There are considerable data not used in this paper indicating a high rate of suicide among cultivated persons. For instance, in the army and navy the suicide rate is greatest among commissioned officers, next highest among petty and warrant officers and lowest among the enlisted personnel. Also, in tables showing the occupation of persons committing suicide, the rate seems to be highest among professional groups and lowest among laborers.

True, the use of vital statistics is difficult. In Massachusetts, however, since 1885 all violent deaths have been the subject of scrutiny by medical examiners, making the figures somewhat more reliable. I was of the opinion that it was not possible to correlate economic depressions with increased suicide rates. However, during the recent depression there has been an astonishing and otherwise unexplained increase in suicide in Massachusetts.

Concerning the mass suicides among primitive peoples, it is difficult to compare the situation with that among civilized races, at least in recent years. Great masses of civilized persons have not been subjected to starvation or pestilence as has been the case with primitive peoples. I think that suicide among primitive persons under these conditions is different from the occasional suicide in modern civilization. One must also consider the contagiousness of emotional expression among primitive persons. I do not see how it is possible to say that there is a "greater propensity to suicide among savage persons than among civilized people" until one is able to study civilized persons subjected to the same situation. Was suicide among the oppressed Indians of the West Indies different from that occurring today among persons awaiting trial and execution? Also, life is held much cheaper among primitive peoples. Again, one must reckon with social custom. Certainly, Benzoni did not wish one to believe that of the 2,000,000 original inhabitants of Haiti all but 150 killed themselves. As for the group starvation mentioned, this may be looked at in another way. The famous case of McSweeney, the Irish patriot who starved himself, is to the point. It is probable that his motive was not primarily self-destruction but that he was making an attack on the British Empire. It is true that in the last edition of Durkeim's book a great deal of the supposed increase in suicide has been shown to be due to greater zeal in compiling mortality statistics.

I agree with Dr. Zilboorg that mental disease is merely one of the causes of suicide and that the old belief that patients with psychoneurosis do not commit suicide is false. The comparisons of suicide and homicide rates in Europe, which have so frequently been used to illustrate racial differences, need careful scrutiny. Studies in Massachusetts tend to emphasize the importance of social custom in this matter. For instance, the suicide rate is low in Ireland but high among the Irish in Massachusetts. The homicide rate among Italians is high, but the rate among Italian Americans in Massachusetts is negligible.

I am not convinced that fantasies concerning death are an important factor in suicide. Death often appears to be an incident in the course of violent expressions of feeling which result in self-injury.

It has been customary of late to speak of the deeper layers of the unconscious. I sometimes wonder if this is not an artificial distinction. If one used

the analogy of the visual field, the focal point of vision being compared with consciousness, would it not be more correct to speak of the remote factors found at the periphery than to weight the value of observations by using the word deep?

The study of method is illuminating, for it tends to show what sort of person one is concerned with and the sort of impression he seeks to create on his associates. One of the references made by Dr. Zilboorg consisted largely of the analysis of messages left by persons committing suicide, showing that even in this matter the actor has his eye on the grand-stand and seeks to justify himself with his associates. A number of interesting cases in Massachusetts illustrate that when this emotion is directly aroused the most primitive reactions occur. Two physicians of distinction who killed themselves a short time ago had every modern method of destruction at hand, yet one stole to his attic, stood on a box and threw a rope over a cross-beam to hang himself. Another went to his closet, fastened a tie to his neck, threw it over a hook and twisted himself about until he was strangled. These and other cases have sometimes led me to believe that suicide is primarily an attempt not to kill but to injure oneself. It seems almost to be a gesture, incidentally causing death. In spite of this, there has been a constant increase in the use of illuminating gas in Massachusetts, showing that in this matter people are gradually becoming civilized.

I doubt whether there is anything in the animal kingdom corresponding to voluntary suicide in man. The tale of the scorpion appears to be a myth, and the dog stories seem to deal only with the remote past. Most instances which can be credited deal with frenzied flights from fear, and death appears to be incidental. Dr. Zilboorg apparently dismisses the examples from antiquity, except for purposes of speculation.

The case of Malinowski, in my opinion, illustrates the tremendous force of public opinion among savages. I had thought of hari-kari as a ceremonial suicide. In suttee and hari-kari, as well as in some other ceremonial suicides, it appears that the person is not motivated by a desire to die but is seeking the approbation of the community by conforming to social custom. Suicide for vengeance appears to be another matter. It seems to represent not a factor of escape but an attack. Perhaps it is involved with the pugnacious instinct and represents retaliation rather than the instinct to flee. There are many stories of various primitive persons who can die voluntarily, but so far as I know these are not authenticated. I think that most physicians have seen elderly persons disintegrating who would have been glad to be assisted toward death if social custom did not forbid.

Dr. Zilboorg stated: "Every voluntary act of suicide, despite its external coat of deliberateness, in reality presents a sort of complicated reflex motor response, the center reflex arc being embedded deep in the racial past in a matrix of intense primitive affects." With this I wish to express the heartiest agreement. It seems to me as fine a statement as I have yet heard. Mankind universally meets emotional stress of varying intensity. Each person has thresholds of varying height which impede the responses aroused, yet when these responses are sufficient they push over the highest threshold, after which man acts instinctively. It may be proper to speak of the instinct to suicide. It certainly could be defended as well as the instinct to self-preservation.

Of the identification with the dead I am somewhat skeptical. When emotions are sufficiently aroused they seem to sweep through as a motor response, with meager consideration of ideals and sentiments. It seems to me that the ordinary person who commits suicide is not particularly trying to join the dead but merely attempting to escape from an intolerable situation among the living. The fact that slaves and wives willingly submit to death at the graves of their masters and lords is evidence of the tenacity with which persons cling to social custom. Perhaps they are trying to join their masters in death. It seems to me that they are trying rather to gain the approbation of their associates in life. Strangulation is an ancient and a common method. This may be due to the fact of its relative ease. I wish to ask some physiologist who is present whether it is possible to kill oneself by holding one's breath.

Nov. 21, 1935

C. A. McDONALD, M.D., *Presiding*

THE MANIC MOOD. DR. NIELS L. ANTHONISEN.

The manic mood is usually regarded as a spontaneous phenomenon in which elation and expansiveness constitute the nucleus, while affects such as anxiety and sense of danger, which are frequently observed, are considered incidental and referable to the fundamental mood. In the present paper an attempt is made to show that in spite of the elation a trend of anxiety is usually in evidence. This is in agreement with the conception that the manic attack is a reaction to a difficult situation and represents an effort on the part of the patient to overcome the difficulties. The mainspring of the manic attack is thus, on the one hand, aggression and, on the other, anxiety. Freud has stated that "work" is carried out during a depression. This can be said with equal justification of the manic attack.

THE MINERAL CONTENT IN CEREBRAL LESIONS, AS DEMONSTRATED BY THE MICRO-INCINERATION METHOD (with demonstration of lantern slides). DR. LEO ALEXANDER and DR. ABRAHAM MYERSON (with the technical assistance of David Goldman).

The micro-incineration method was first devised by the French pathologist A. Policard, who applied it especially to the study of tumor tissue. Later the method was revised by Dr. G. H. Scott. In our work we followed Scott's modification of the method and the general technical rules laid down by him. Dr. Scott had a furnace constructed in his laboratory and sent to us, which we used in most of our work. In the latter part of the work we also used furnaces which now are manufactured by the A. S. Aloe Co., St. Louis, according to Dr. Scott's procedure.

The micro-incineration technic consists in exposing sections of tissue fixed in a mixture of absolute alcohol and formaldehyde (9:1) and cut at a thickness of 4 microns to temperatures up to 650 C. By this procedure the organic components of the section are burnt and only the mineral constituents remain on the slide. The sections can be studied with dark field illumination.

With this method Policard, Schultz-Brauns, Scott and Cowdry studied the normal anatomic structure and pathologic changes of a great number of tissues of man, vertebrates and invertebrates. Data on the nervous system, however, are still scarce. Scott studied the localization of mineral salts in the normal nervous system of some mammalia. Covell and Danks studied the Negri bodies in cases of rabies. Patton studied the cellular disease in experimental poliomyelitis and observed that after a transitory stage of increase in mineral content the diseased anterior horn cells became demineralized.

In our studies we collected a larger number of normal specimens and a greater variety of pathologic conditions and cerebral lesions of the human brain than have hitherto been examined.

It is a common belief that minerals in brain tissue appear especially where tissue has undergone necrosis. This contention, however, was not borne out by our studies. Minerals in the human brain are inborn. Sections from the brain tissue of a premature infant show a great amount of mineral in the ganglion cells of all cortical layers, which, however, in contrast to the arrangement in adults, is accumulated in the nuclei of the ganglion cells. It will be seen later also that other actively growing tissues, especially tumor tissues, show nuclear mineral deposits. In the adult, however, the mineral deposits in ganglion cells are restricted to the cytoplasm and the nucleolus, while the nucleus itself is free from minerals. In the human cerebral cortex the pyramidal ganglion cells are much richer in minerals than the granular cells, which are very poor in them. Further, the large motor ganglion cells in the spinal cord contain substantial mineral deposits in the nucleolus and cytoplasm, while the nucleus is free from

them. The mineral deposits in the cytoplasm are globular, and, as demonstrated by stained sections used as a control, they correspond in their arrangement to the Nissl bodies. The dendrites are also rich in mineral content, while the axis-cylinder and the collicle of the axon contain little.

In spinal cords of cats which have been subjected to experimental dehydration, as shown by experiments which were carried out in collaboration with Dr. W. E. Patton, the globular mineral deposits undergo dusty degeneration, and in some instances the deteriorating ganglion cells are clasped by proliferating neuronophagic oligoglial and microglial cells, the nuclei of which are extremely rich in minerals. In some instances the mineral deposits of the affected ganglion cells shift from the globular Nissl bodies into the interglobular spaces, which are normally occupied by the neurofibrils. In later stages the centers of the cells become demineralized, while the minerals accumulate along the edges of the cells. The affected cells become round and have a swollen appearance, comparable to that of the cells in pellagra. In later stages the cells are swollen and round and are completely demineralized.

In the normal cerebellum the richest mineral deposits are observed in the granular cells, while the Purkinje cells contain a sparser amount in the cytoplasm and dendrites. In some instances Cajal's baskets are observed to be outlined by the mineral granules which they contain. The presence of richer mineral deposits in the granular cells of the cerebellum is in contrast to the condition in the cerebrum, where the granular cells contain the least amount of mineral. This indicates that the granular cells in the cerebrum and those in the cerebellum are fundamentally different in chemical composition.

The ependyma is normally rich in minerals, and its mineral content increases greatly in cases of granular ependymitis. The amyloid bodies are rich in minerals and stand out along the edges of the central nervous system as homogeneous bright bodies of high mineral content.

The collagenous fibers of the walls of the cerebral blood vessels are fairly rich in minerals. The elastic layers, however, are devoid of minerals. In arteriosclerosis the collagenous fibers within the newly formed proliferation of the intima are rich in minerals, though less rich than the older fibrous material in the outer portion of the wall. In cases of this disease the inner elastic membrane, which can still be seen as a dark, nonmineral-containing layer, appears to be perforated by a great number of fine, mineral-containing collagenous fibers, which connect the intimal proliferation with the outer part of the intima and media. This confirms Ranke's observations on the fenestrations of the elastic membranes, especially concerning the increase of these fenestrations in association with arteriosclerosis and related vascular diseases.

In thrombosis of vessels in the cerebrum the fibrinous network in the early stage shows a very faint content of mineral, while the granulation tissue of the organized thrombi is very rich in minerals, especially around recanalizations.

Foci of softening appear as demineralized areas in which only the scavenger cells stand out as isolated bodies of high mineral content. Hemorrhages are strikingly rich in mineral. The mineral deposits in areas of hemorrhage show as reddish yellow in the dark field, probably due to the presence of iron. However, this will have to be confirmed by further microchemical analysis.

These observations in cases of hemorrhage led us to consider also the mineral content of normal blood. Normal blood smears show most of the mineral to be accumulated in the nuclei and cytoplasm of leukocytes, in the nuclei of lymphocytes and in the blood platelets. Especially do the platelets stand out as having a high mineral content. The red cells contain a moderate amount of mineral, which in most instances is visible only along the edges of the cells, thereby giving the appearance of a ringlike arrangement. In a case of myeloid leukemia the nuclei of the myeloblasts and, to a less extent, the cytoplasm appeared to be rich in minerals.

In purulent meningitis the meningeal exudate is extremely rich in minerals, in comparison to which the brain appears dark and poor in mineral content. Also, tumors can be immediately recognized as rich in mineral-containing substances, in contrast to the normal brain tissue, the mineral being accumulated especially in the nuclei but present also in the cytoplasm of the tumor cells.

Plaques of multiple sclerosis stand out as demineralized areas in the brain, and in their mineral architecture closely resemble foci of softening. In early hyperemic plaques engorged capillaries are conspicuous as highly mineralized spots in a demineralized area, as are the cell bodies of the macroglial protoplasmic astrocytes in these lesions. The macroglial astrocytes are especially well outlined against the demineralized background of the plaque and give a picture comparable to that of specimens prepared by Ramón y Cajal's gold sublimate method. The engorged small blood vessels and capillaries contain in their adventitial spaces a great number of large phagocytic cells which are very rich in reddish yellow mineral granules and which, as already mentioned, probably contain iron. In the older anemic plaques, which also stand out as grossly demineralized areas, many of the smaller blood vessels are obliterated or thrombosed, while against the demineralized background of the plaque well outlined large, mineral-containing fibrillary astrocytes can be seen. These results confirm the observations and support the theory of Dr. T. J. Putnam, who first recognized the plaques of multiple sclerosis as simple, bland regressive lesions obviously of vascular origin.

In senile dementia the plaques do not show excessive mineral deposits or demineralization. They do not stand out in incinerated slides, and they could hardly be seen without the use of adjacent sections stained by Bielschowsky's method as controls. With the aid of such slides, however, the plaques can be localized and identified as a slight disarrangement of the glial reticulum, which, however, is neither poorer nor richer in minerals than the rest of the glial ground net of the tissue. These observations tend to disprove the theory of von Braunmühl, who explained the senile plaques as inorganic mineral precipitates, and to some extent they favor the theory of Bouman, who explained them as areas of metaplasia of the glial reticulum. We conclude from our studies that senile plaques are of organic nature and do not contain mineral deposits, because they burn in micro-incinerated slides.

Alzheimer's neurofibrillar strands, however, are well demonstrated in micro-incinerated slides and stand out as amply mineral-containing interlaced strands, while the rest of the cell, the nucleus as well as the cytoplasm, is demineralized.

We have not yet been able to identify the various types of minerals observed in our specimens, with the possible exception of iron. The finer analysis must be left for further study.

Reduction of Postencephalographic Symptoms by the Inhalation of 95 Per Cent Oxygen. Dr. Robert S. Schwab, Dr. Jacob Fine and Dr. William Jason Mixter.

This article will be published in full, with discussion, in a later issue of the Archives.

PHILADELPHIA PSYCHIATRIC SOCIETY

Regular Meeting, Nov. 8, 1935

Joseph C. Yaskin, M.D., President, in the Chair

The Past and Present Trends in Research in Mental Disorders. Dr. Nolan D. C. Lewis, Director of Laboratories, St. Elizabeth Hospital, Washington, D. C.

An attempt is made in this paper to analyze the various aspects of psychiatric research and to offer some general principles and specific ideas for future procedure. In the past the medical profession has felt a lack of scientific unity; apparently it is now more keenly aware of being confronted "with the problem of the person and constitutional pathology, with the concept of disease, the norm and different degrees of responsiveness, with the sensitivity of the organism as a basis for its response to therapeutic measures, with the natural recovery from disease" and with the psychic aspect of disease problems.

Inherent or Intrinsic Difficulties in Psychiatric Research.—In the phenomenon of life the parts and the whole are not in opposition but belong together and exhibit in each particular characteristic a pervasive polarity. Professor Baglioni, of Rome, at a medical congress in 1933 emphasized the great differences in persons and pointed out that methods which are purely morphologic and statistical do not express the biologic reality of person, the essentials of which are variation which defies all attempts at mathematical determination. The phenomenon of variation is one of the main features in all aspects of integration. It is a quality of living matter on which evolution progresses, and as evolution at present is probably most active at the mental levels of integration one perhaps should expect the highest degree of variation in whatever constitutes mental behavior. The definite directions taken in mental evolution are not explained adequately by natural selection, inheritance of acquired characters or any theory of purposive design. Variables, which are complex in all biologic activities, are greatly increased at the psychologic level. In all living forms they have to do with the principle of adaptation.

Adaptation as here considered is concerned with living material composed of biologic patterns and systems, functioning in a type of complexity which renders exact measurement, as it is understood in many sciences, difficult if not impossible; herein lies one of the inherent difficulties which explain the paucity of reliable results obtained with physicochemical methods when applied in psychiatric investigation.

Quastel has recently (1932) outlined this category of difficulties as follows: 1. Observational or experimental study is different from other branches of research. 2. Mental disease is an expression of underlying conditions, the sites, details and causes of which in the majority of instances are either unknown or are far from clear. 3. Physiologic abnormalities may differ greatly among persons exhibiting mental disorder. The difficulty for the physiologist is the confused state of taxonomy. For this reason workers have turned to the more psychogenic aspects of mental disease, in which something more tangible can be analyzed and understood in psychologic terms. One can determine how mental processes interact and build up the symptom complex recognized as a neurosis or a psychosis. The psychologic causes of a mental disturbance become understandable in psychologic terms and on certain basic assumptions. 4. Another difficulty is that biochemical observations must be confined largely to human material. This obviously involves a great restriction.

There is evidence to show that the laws of the mind and of the body relationships are the same, but what one needs to demonstrate and learn is the nature of the difference between the "lower" and the "higher" integrations within these laws.

Imposed Difficulties in Psychiatric Research.—Man, by his particular construction of moral codes, customs and tribal taboos and by his avidity in the dissemination of precocious and perhaps unscientific ideas on inheritance, has imposed a handicap on psychiatry from its inceptive stages.

1. In the creation of psychologic theories investigators have wandered unnecessarily from fairly well established biologic principles, and the power of complex terminologies has contributed greatly to the general confusion. The greatest care must be exercised to avoid the indiscriminate application of concepts borrowed from one field to another and particularly from one level to another. Information from one level of integration may apply only in part or not at all to a different level.

2. There has been an inability or unwillingness to see or to face the research situation as it presents itself for solution. It is necessary to apply experience and knowledge in removing some of the inhibiting concepts as to approaches to research and as to types of methodology.

Approaches to Research.—All clear thinking must involve a direction, an adaptation and a criticism. In approaching the problem of psychiatric research one must

consider the following questions: Is it possible to explore this field with its many obscurities by means of existing methodologies characteristic of the chemical, physiologic and experimental psychologic sciences? Is the psychoanalytic method with its biogenetic and ontogenetic aspects, as usually carried out, adequate for the situation? Can one find indicators, and "indicators" only, of the direction to follow in the existing methods of observational and experimental approaches, or will an entirely new method of approach have to be devised—one that will dissect integrations into their component parts? In the integrations of this field perhaps all of the original aspects of the elements composing them are changed into a new set of characteristics, recognized as yet only partly if at all.

1. The Physicochemical Approach: There are several aspects of living material which have so far resisted any comprehensive physical analysis. Among these are the possession of impulse, irritability, self-identity, unity, aim or directness, adaptation and norm, and the sum of the constants of each.

More work is needed immediately on constitution, for despite the thousands of researches on constitution scarcely one has approached the problem in a global fashion. Many years ago John Hunter summed up the situation as I should like to see it applied today in active principle. He said: "Some physiologists have it that the stomach is a mill, others that it is a fermenting vat, others again that it is a stew pan, but in my view of the matter it is neither a mill, a fermenting vat, nor a stew pan, but a stomach, gentlemen, a stomach."

Several aspects of research on those parts of the personality not yet susceptible to exact measurement, such as that done in psychobiology and psychoanalysis, are scientific if carried on according to certain rules laid down by science. According to Johnson (1934), scientific analysis is the process of separating observations, arguments and conclusions into their constituent parts, the tracing of each part back to its source and the testing of its validity for the purpose of clarifying and perfecting knowledge.

2. The Creation of a New Science: There is a deep gap between the physicochemical integrations of the body and the societal behavior of the human organism. Thus one is confronted with a real challenge in psychiatry, a biologic problem with distorted constellations, now known as dementia praecox, manic-depressive psychosis, paranoia, epilepsy, suicide and criminality, to mention a few of the unsolved features. Although present technics, both psychologic and physicochemical, have not been exhaustively applied and consistently carried out, there is evidence that they are inadequate to solve the fundamental problems, and as the historical pathway of philosophic and scientific thought is literally strewn with discarded hypotheses and theories, investigators have perhaps become too shy, too conservative or too determined to get down to exactly what has happened and thus have been afraid to identify themselves with working hypotheses. They have been too "squint-brained" to be able to recognize the great stimulating value of many discarded hypotheses. These minor defeats must be ignored.

What is needed now is new methods, new points of view and a reassortment of topics and problems. This might be brought about by the cooperation of two sets of frontier workers: a group of those who think, flash thoughts, emanate ideas, and see problems everywhere and another group of more practical-minded pioneers who will take the ideas that seem worth while and build them into experimental applications—to sink or swim in an actual research situation, where the rigid standards of the scientific world may be adequately met.

Judging from what has already accrued in the field of the social, psychologic and psychopathologic sciences on the one hand and from the factual information gained in the physicochemical laboratories on the other, mental disorder is created by what might be called a set of external "instabilities" acting on a set of internal "instabilities." In my opinion the recent trend in the direction of bringing these two main types of methodology near to a common ground is a most hopeful inclination, particularly as it has been autodynamic or spontaneous on the part of those concerned with the work.

Whenever two sciences or branches of science blend, something new is formed. It is a new science so to speak, with fresh methods, special apparatus for experimentation and unique points of view which lead to the discovery of new facts, relationships and criteria.

Some Aspects of Research Promotion.—1. The Securing of Funds: Vast sums of money are spent by federal and state governments as well as by private estates on all sorts of research; a certain portion of this money is invested in medical research. However, comparatively nothing is given for psychiatric research, even by physicians themselves. (Of the grants made by the American Medical Association for 1934, totaling the modest sum of $13,128, only $1,796 went to neurology and nothing to psychiatry.) Billions are spent on the physical care and protection of psychotic patients, but nothing for investigating cause and prevention of psychoses. Who is to blame? The psychiatrists chiefly. They have not concerned themselves with the necessary angle of research.

Much of so-called research, especially subsidized research, is barren of useful results because, as Sir Walter Morley Fletcher, secretary of the British Medical Research Council, aptly put it, "Too often gifts are bestowed on isolated bodies not in a position to frame any effective or long sighted policy or are given for a frontal attack on a named disease. . . . If I had $5,000,000 to spend on medical research I should . . . employ it in developing particular applications of primary physiology and biochemistry which would assuredly bear fruit later on. The new method or new clue that has developed to conquer a disease again and again emerged from studying something else."

2. Problems of Personnel: It is not possible to purchase research work directly. Many intelligent people are apparently not aware that it is a special kind of creative work; the proper conditions are obtained only after securing men with a particular type of imagination. These men must have had the right training and must now have intellectual freedom to follow their own clues. A number of the most promising men are now available for research in psychiatry; they are teeming with problems. The time is ripe.

3. Clinical Research: There is dire need of objective clinical research to prepare the ground for the utilization of supportive sciences. Those who are inclined to see little in ordinary clinical research should stop and consider. "There will always remain a wide domain of problems that we can only solve by watching, recording and tabulating the great age long and world wide experiments nature has always made and will continue to make wherein control disturbs the conditions of normal happenings, and where we can only observe and interpret data which we had no hand in making, but which are given to us" (G. Stanley Hall).

Present Trends.—In discussing present trends in research a few glimpses of the more recent past, from 1920 to 1934, are included. A review of the literature containing the words "dementia praecox" or "schizophrenia" may serve as a general example of the published trends for the whole field of psychiatry. Many psychiatrists have written or said in effect that when the story of dementia praecox is written it will be the history of psychiatry.

There have appeared 1,778 books, monographs and papers, distributed through 12 languages. These were classified under the following captions, which are listed in numerical order: clinical psychiatry, 730; organic or extraneural pathology, 232; pharmacology and pharmacodynamics, 189; biochemistry, 162; neuropathology, 152; neurophysiology, 96; heredity, 78; endocrinology, 68; psychoanalysis, 47, and criminology, 24. In making a survey for ideas regarding research on dementia praecox, 178 laboratory, hospital and other scientific centers were visited, and contacts were made with several investigators in each organization. The first general impression gained from a survey of this character is that research is in a state of chaos, i. e., formlessness—an expression which does not apply to the activities of a single person or group but to the general field. The second impression is that the field may be divided roughly into workers who consider that mental

disorder penetrates from without and those who think that it develops within the patient. Even those who have a more global point of view and who include both general sets of factors formulate problems which are based on either the "psychogenic" or the "organic" aspect, to use a current terminology.

The problems proposed for future investigation include a wide variety of approaches, in many of which new technical methods are utilized. Although all of the problems come to a common focus, which is directed toward an attempted explanation of the pathologic behavior of the patient, each type of study has its individual technic and working hypothesis and emphasizes certain aspects of the situation.

Those who are oriented in the direction of the environmental and more particularly the societal factors in the environment would advise the following procedures, which have been listed under general headings and subheadings:

General Environment

1. "Epidemiology:" the geographic distribution in community, county and state backgrounds
2. Selected group studied simultaneously for economic, religious and moral life factors
3. The mother-child relationship in cases of schizophrenia
4. Differences in capacity for effective rebellion
5. Study of behavior by means of the play technic
6. Phenomena of ambivalence between parents and children
7. The various aspects of amaternalism
8. Creation of a special experimental and therapeutic environment supplemented by chemical, physiologic and psychologic studies (for adults, adolescents and children)
9. Research among primitive people—Bali

Special Psychoanalysis

1. Quantitative psychoanalytic technic
2. Psychoanalysis of children
3. Intense psychoanalytic study of a few selected patients
4. Comparative psychoanalytic technic with ordinary hospital care

Clinical Differentiation in Adults

1. "Day by day" detailed behavior observations and recordings
2. Study of "experience variables" technic of Chassell
3. Mechanisms of hallucinations—eidetic imagery
4. The "natural history" of the development of the disorder
5. Clinical clarification of the concept of dementia praecox subtype groupings, tentative, previous to research, to be rearranged after group research
6. Special studies of psychotic symptoms in those with neurologic lesions and general medical diseases
7. Recovery versus malignant reactions in the postpartum psychoses

Clinical Differentiation in Children

1. Prenatal and postnatal reactions and types of children, including a study of the mothers
2. Complete behavior, educational, social, physical and biochemical studies (Bradley type)
3. Clinical, biochemical and therapeutic differentiation of benign and malignant reactions in problem children
4. Aggression situation in cases of schizophrenia
5. Longitudinal study of "schizoid" children—fifteen years' investigation

6. Case report and "follow-up" studies of patients with mental diseases who were seen as children in the child guidance clinics

7. Differentiation between children with dementia praecox and feebleminded children

Problem Trends in Psychology

1. Differences between "organic" and "emotional" deterioration

2. Investigations with the Rorschach test

3. Language analysis with Vigotsky test—associative processes—reasoning and projection peculiarities

4. Language studies on types of schizophrenic thought, syntax, speech and logic

Those who are more "organically minded" or who place emphasis on constitutional factors have the following types of problems in the foreground for investigation:

Heredity

1. Inheritance of psychologic and temperamental patterns (comparative psychology)

2. Study of heredity through the female line

3. Comparative studies on heredity and environment (material from the Bloomingdale Hospital, White Plains, N. Y.)

4. Studies of pedigrees—accumulative

Constitutional Elements

1. Biometric and general constitutional studies of the families of schizophrenic patients

2. Constitutional differences in motor responses

3. Methods of determining the plastic and rigid types of nervous system integration

4. Habitus studies

5. Repetitions and refinements of Kretschmer's Körperschema work

Organic Factors—Chiefly Extraneural Pathology

1. Various experiments to throw light on the circulatory functions in the brain and other parts of the body

2. Metabolic changes in childhood

3. Relationship of tuberculosis and polyendocrine sclerosis to dementia praecox

4. Peripheral circulatory responses—vasodilatation and blood flow, etc.

5. Relationship between syphilis in the family and dementia praecox

6. Effect of rickets on behavior and development of the nervous system and lesions in the nervous system

7. Allergic reactions of various types in patients with dementia praecox

Neuropathology

1. Histologic investigation of the region of the third ventricle

2. Examination of the vagal nuclei and tuber cinereum in persons dying in acute stages of catatonic excitement and stupor

3. Histophysiopathology of the thalamic region in accordance with Cannon's theories on emotions

4. Study of the cortex by the new "freezing" and "drying" methods

5. Histospectroscopy—cytology of the cortex

6. Study of cortical areas by means of the cerebral biopsy technic

7. Special studies on the pathology of the microglia

8. Comparison of the neuropathology in acute catatonic states with that in a variety of toxic conditions

9. Comparison of the neuropathology of "organic schizophrenia" with that of less complicated schizophrenia

General Biochemistry

1. Studies on the effect of insulin on dementia praecox states (Saxel and Schnester)

2. Various endocrine surveys—total and partial

3. Blood as a colloidal system

4. Experimental procedures with the filtrable viruses

5. Growth-promoting substances as developed in tissue cultures

6. Assay of hormones and antihormones by chemical and tissue culture technics

7. Researches on the androgenic and estrogenic hormones

8. Permeability of the cerebrospinal fluid barrier and nature of the "bromide ratio" (serum and cerebrospinal fluid) by electrometric methods—ultrafiltration methods

Neurochemistry

1. Differential chemistry of the brain areas—a long research on normal and pathologic variations

2. Special problem of the distribution of creatinine in the brain and spinal cord.

3. Oxidation and reduction neurochemistry

4. Detailed chemistry of nerve activity

5. Metabolic studies on the central nervous system—studies of vitamins.

6. Physical chemistry of membranes

Physiology

1. Myogramic studies on fatigue

2. Investigations on perceptive resistance (audiometer) types

3. Electrophysics of afferent impulses

4. Electrophysics of nerve cells

5. "Phase angle" of body (Johnson), a new technic developed in connection with basal metabolic studies

6. Electrophysical studies on variations of electric potential

7. Chronaxia of the whole body and of parts of the body

8. Electro-encephalographic investigations with numerous variations in technic and applications

9. Cathode ray oscillographic method of studying brain action currents.

Pharmacology and Pharmacodynamics

1. Pharmacology of the vegetative nervous system in acute psychotic reaction types

2. Pharmacoanalytic research and therapy

Miscellaneous

1. A complete survey of anthropologic and ethnologic literature

2. Complete evaluation and synthetic study of the literature to avoid the mistakes made by others, to determine what has been done and to make important correlations and deductions as to future procedure

3. Correlated "individual statistics" on biochemical, physiologic and sociologic aspects, i. e., many types of studies on the same individual case

4. Suicide in dementia praecox

DISCUSSION

DR. C. W. BURR: Dr. Lewis' presentation contains a definite proposal of work that is to be done. Many investigators are showing that it is planned and not a dream. The work will be controlled from the Neurological Institute in New York, which means that it will be satisfactorily controlled. All my teaching life I have had trouble with students who were bright, because all of them asked me questions. The ingenious youth always thinks that his teachers are omniscient, but I am always being asked questions that I cannot answer. This has continued for thirty-six years and is the fault of my ignorance, which is the result of the ignorance of the men who taught me. I am almost beginning to think that whatever it is that controls this human universe takes a sort of impish joy in making the mind of man perform in such a way that psychiatrists will always be in trouble. Sometimes I am almost sure of this. The classification of diseases is worse than chaos. I do not believe that in twenty-four years from now (when I think something will be known) the term "dementia praecox" will be in use. I do not think that many of the diseases to which names are now given will be regarded as diseases then. When I began to teach it was still taught (and I myself had been taught) that mental disease was an illness with a definite cause, a definite course and a definite morbid anatomy. "Dementia praecox" was largely "adolescent insanity;" frankly, I think that "adolescent insanity" is the better name because the condition has its origin in the protoplasm of man and is a defect in the development of man. I was much interested in what Dr. Lewis said about some patients in institutions for the feebleminded probably having a psychosis in its early stage—a breakdown in mental machinery that before was good machinery. I am sure that it is true. I am a pessimist, but many things have happened through the years of my professional career. I think that psychiatry was blackest fifty years ago, when I was a student. Chemical discoveries, one after another, have been revealed. Almost all improvements that have been made in psychiatry in my generation have been along biophysiochemical lines, and that, from my point of view, is the line in which more and more progress will be made. I do not think that the study of the mind by metaphysics or the interpretation and classifications of strange dreams is ever going to work. The test tube, the microscope, the study of physical laws—those things will help.

DR. EARL D. BOND: It must have been a help to the 178 institutions to have known Dr. Lewis and to have been asked questions. If he had done nothing more, the study would have served to coordinate the ideas of persons in scattered places. He seems to have made this investigation without prejudices. Of course, I cannot conceive that there is any one answer to all the questions that Dr. Lewis has raised in his paper. I shall confine my remarks to one way of building up a longitudinal and cross-sectional study of dementia praecox in its growth.

For instance, two children at the Franklin school have been studied for about a year. In that year, by day and night observation, a cross-sectional picture was built up in detail of a psychosis in a child at the age of 9. The child's thoughts were also described. One can go back directly to the child's infancy, because the brothers and sisters, the father and the mother and the family physician are available for questioning and none of these persons have to remember very far back. It is possible to go forward because reports have just been received from two hospitals, one in this state and one in New York; they describe these two children in stages marked by catatonic symptoms and by some of the mental behavior which is apparently usually associated with dementia praecox. It will soon be known whether these girls have dementia praecox or not. If they have, there will be a continuous, preserved record from infancy. In one of the cases there is a record of biting and scratching when the child was nursing at the breast at the age of 8 months; these biting and scratching episodes continue now at 16 years, when the child has a near dementia praecox condition.

DR. E. A. STRECKER: The high points in the history of this project for the investigation of dementia praecox will be of interest. There had been in existence

for some time a committee, the so-called scientific committee of the National Committee of Mental Hygiene, made up of about 6 psychiatrists from various parts of the country who met solemnly once a year or so, had a dinner in New York and made some general suggestions about research if anybody ever gave any money for research. About a year ago Mr. Melvin Johnson, Sovereign Grand Commander of the Supreme Council, Thirty-Third Degree Masons, indicated that a part, and perhaps eventually the whole, of a sum of $3,000,000 might be available for a study of dementia praecox. Mr. Johnson had himself arrived at a conclusion that this particular disease is a worth-while target for investigation. I believe that the income of the fund before that had been used for educational purposes; it had been decided that the results of the education were so bad that it should be abandoned. Mr. Johnson then spent some years, with help, collaboration and advice, investigating various disease problems. I believe that in the course of the study he narrowed the choice down to tuberculosis, carcinoma and dementia praecox; he eliminated the first two and felt convinced that this condition called dementia praecox is the outstanding disease problem of civilization, a conclusion with which I agree. Then the committee began to meet frequently, sometimes a couple of times a month; one of the first things the committee did, and perhaps the wisest, was unanimously to choose Dr. Nolan Lewis to be in charge of the project, the preliminary phase of which was to select centers of research throughout the country. Dr. Lewis has performed that task with amazing soundness and thoroughness.

With Dr. Lewis' help, the committee first abolished the schizophrenic curse, which is a kind of notion that persists, and may be true (though I do not believe so) that the problem of dementia praecox is not solvable. That was said and has been said of every disease problem which has since been solved. It was decided, after advice was received from various parts of the country about the importance of first defining dementia praecox, that there would be millions, and it was hoped three millions, for research, but not one cent for definition. The committee felt, as Dr. Lewis has indicated, that definitions, if they are made, will come after research has advanced to some definite point. It was felt that if the money was spent to obtain a definition, and it would be easy to spend $3,000,000, the problem might still be unsolved. It was decided that what at first glance would seem to be a very attractive method of investigation was after all of no value. That method is to take persons who have this condition called dementia praecox and examine them thoroughly from head to foot—color of eyes, color of hair, blood sugar, etc., as has been done before in many other conditions. The net result has been nothing, because I presume that there is a fundamental condition operating which defeats that kind of research. A person is not merely the sum of his parts With this in mind it was decided not to spend money in that way. Then the committee arrived at the idea that the research should not be done in one particular place; that while something would be gained by organization, etc., something more would probably be lost, because, after all, all the investigative brains in the country would scarcely be massed in one particular geographic locality. Then certain ideas came out of the first meeting of all the men. Dr. Lewis felt strongly that children provided an opportunity for research along the lines that Dr. Bond has indicated and along other lines. The committee wanted to be extraordinarily careful, and I am happy to say that that was true of all the men who also had strong psychoanalytic tendencies. Dr. Lewis has told something about his work. He has told it with his characteristic modesty. He has said nothing about his own important contribution to this problem, which happily will be continued in this investigation. His contribution to the problem is to present the problem of neuropathology and other important features that are, of course, outstanding in research in this field.

Some interesting facts have arisen from Dr. Lewis' investigation. He went to practically every part of the country. It was interesting that if all the projects which were offered for the investigation of dementia praecox could be financed, everything could be done for $500,000. It was also interesting that

Dr. Lewis had remarkably few, comparatively speaking, proffers concerning psychoanalytic investigation as compared with the other lines of investigation. I learned things about Philadelphia from Dr. Lewis that I did not know. Philadelphians do not know much about the opportunities there are here. At one meeting Dr. Lewis said to the committee: "Gentlemen, I know after my visit to Philadelphia that the best laboratory of medical physics in the United States is in Philadelphia." I did not know that, and I was glad to have it pointed out to me. That laboratory is the Johnson Laboratory of Medical Physics in the University of Pennsylvania. Perhaps I should not say much about this, but if Philadelphia psychiatrists felt friendly before toward Dr. Lewis they ought to feel doubly friendly now because, after all, his influence in the final allotment in research projects was considerable. As it happens, of the first allotment of money distributed, I think in something like eleven states, about 40 per cent comes to Philadelphia.

Dr. Nolan D. C. Lewis: Dr. Burr said that this research work, some aspects of which I have mentioned, is to be controlled through the Neurological Institute. That is not quite the word for it. All research workers will have complete intellectual freedom and will direct their own problems. It may be that some attempt will be made to coordinate the results or to see that things are going along in an effective manner as far as possible. I have been retained as general coordinator, but any one who is doing research in the organization can feel sure that there will be no control of his activities as such.

The second point that I want to emphasize again is the one that Dr. Bond raised about the benign and malignant features of dementia praecox as they appear in children. That is really a cross-roads situation. There is no way of finding out what the outcome will be in a child, i. e., whether it will be a malignant outcome eventuating in permanent hospitalization or whether the condition will disappear, except by continued observation. The type of work that Dr. Bond is very skilful in doing is differentiation, which eventually, I am sure, will lead to knowledge of which symptoms imply a favorable and which an unfavorable outcome. When one studies the histories of feebleminded children in institutions, one finds, of course, those who have been feebleminded from birth and also a number (I do not know how many because it is apparently only in recent times that those dealing with the feebleminded have been convinced of this difference) of children who were well until 4 or 5 years of age and seemed to be learning efficiently; the failure came in the early school years. Some have thought that these children have an early type of deterioration; at least, the etiology must be different from that in the congenitally feebleminded children. A differential psychologic, physiologic and chemical evaluation is important.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, Nov. 12, 1935

Israel Wechsler, M.D., *President of the Neurological Society, in the Chair*

Trichiniasis of the Nervous System. Dr. Harry Most and Dr. Milton Abeles (by invitation).

This article will be published in full in a later issue of the Archives.

Tumor of the Posterior Fossa Without Papilledema. Dr. Ira Cohen.

Seventeen of 35 patients with tumor of the posterior fossa (other than intrapontile) entered the hospital without measurable swelling of the disks. The variety of the lesions represented a cross-section of the usual distribution of growths in

this location. There were 3 tumors of the acoustic nerve, 2 meningiomas, 4 medulloblastomas, 2 hemangiomas, 1 hemangio-endothelioma, 2 spongioblastomas, 2 metastatic tumors and 1 tuberculoma. In 14 patients the ventricles were dilated; in some the dilatation was extreme. I question whether there is not some factor in addition to increased intracranial pressure that causes papilledema. The absence of choking of the disks does not rule out a diagnosis of a tumor of the posterior fossa, nor does it favor the diagnosis of an intrapontile growth.

DISCUSSION

DR. MOSES KESCHNER: Dr. Cohen well emphasizes the important fact that a tumor of the posterior fossa may attain considerable size and cause marked hydrocephalus without producing papilledema. Although this is generally appreciated by neurologists and neurosurgeons, the members of the medical profession at large do not seem to be fully aware of it, with the result that too many patients with tumor of the brain are treated for a long time for sinus disease, neurosis or some other condition and are not referred to the neurologist or the neurosurgeon until the papilledema is well established and vision is perhaps seriously impaired. From a reading of most textbooks on neurology one obtains the impression that papilledema is an early sign of tumor of the posterior fossa. Dr. Cohen's statistics, as well as those from other clinics, should serve to dispel this erroneous idea. Dr. Cohen stated that in practically all of his 7 cases of tumor of the posterior fossa the fundi were normal and that in a few cases there was engorgement of the veins, a little hyperemia of the disks or some haziness of the margin, suggesting that the eye was not absolutely normal. The neurologist is familiar with this type of disk, and usually he refers the patient to the ophthalmologist with the specific question whether it is indicative of intracranial hypertension or is due to some toxic or infectious process. It has been my experience that it is difficult to pin the ophthalmologist down to a definite opinion as to its pathologic significance. I wonder whether an examination of a fundus of this type by means of the Gullstrand binocular ophthalmoscope might not show some changes which cannot be revealed by the ordinary ophthalmoscope. Koeppe (*Arch. f. Ophth.* **109**:454, 1922; **99**:121, 1919) has done some work along this line and has expressed an opinion that edema of the disk can be recognized much sooner with the Gullstrand binocular ophthalmoscope than with the ordinary ophthalmoscope. However, equally eminent ophthalmologists deny this. I believe that it would be profitable if neurologists would cooperate with ophthalmologists in a reinvestigation of this problem.

All must agree with Dr. Cohen's statement that neither the duration of the disease nor the location, size and consistency of the tumor nor the degree of intracranial hypertension nor the size of the ventricle found at operation or necropsy offers an explanation for the absence of papilledema in his cases of tumor of the posterior fossa. It is obvious that until more definite knowledge is available as to what causes papilledema one will not be able to explain its absence in such cases. That intracranial hypertension is not the sole cause of papilledema is well known. The fact that elevation of intracranial pressure by no means always causes papilledema, as, for example, in children with chronic hydrocephalus, even in those whose sutures are already united, and also the rarity of papilledema in many cases of meningitis in which the intracranial tension may be unusually high, as well as the presence of high grade papilledema in cases in which the intracranial pressure is not very high, would seem to be fairly good evidence that intracranial hypertension is not the sole factor in the production of papilledema.

Recent work by Paton and Holmes (*Brain* **33**:389, 1911), L. Paton (*Tr. Ophth. Soc. U. Kingdom* **42**:104, 1922), Parker (*J. A. M. A.* **67**:1053 [Oct. 7] 1916; *Tr. Am. Acad. Ophth.* **29**:77, 1924; *A. Research Nerv. & Ment. Dis. Proc.* **8**:256, 1929) and others on the relation of intra-ocular pressure to papilledema has shown that a difference in the tension of the two eyes is a determining factor in the onset of papilledema, which usually appears first in the eye with the lesser tension; when the tension in the two eyes is equal, the papilledema develops at the same time and is of the same degree.

Recent experimental data would also seem to support the idea that an increase in the diastolic venous pressure in the retina and its relation to the diastolic retinal arterial pressure are decisive in regard to the production of papilledema. When arterial retinal tension is low, even a slight increase in the venous retinal pressure caused by intracranial hypertension gives rise to papilledema.

It is therefore apparent that before one can answer Dr. Cohen's question as to the cause of papilledema one will have to know more precisely the relationship between retinal circulation, intra-ocular tension, errors of refraction and increased intracranial tension. Until then, the clinician must study each case in which tumor is suspected and determine the presence or absence of tumor of the brain with the diagnostic methods in vogue, bearing in mind that while papilledema is in most instances diagnostic of tumor of the brain too much weight should not be attached to its absence, even though the tumor is thought to be in the posterior fossa. In a case in which the diagnosis of tumor is doubtful it is often advisable to subject the patient to aerography rather than to wait for the appearance of papilledema. I think that this is the safest procedure as far as the patient is concerned.

DR. FOSTER KENNEDY: I understand that Dr. Cohen did not report the refractive condition of his patients. It is known that only a slight degree of myopia is sufficient to prevent the development of papilledema for a long time and perhaps permanently. The anatomic arrangement of the papillae in the posterior orbital wall is such in cases of myopia as to take away the fluid collected on the nerve head, so that it may never become visible to the ophthalmoscopist. A myopic person with a high degree of intracranial pressure may never have papilledema.

Dr. Keschner spoke as if it were difficult to determine whether a congested and pink nerve head is the seat of beginning papilledema or the seat of toxic optic neuritis. Toxic neuritis that is of a sufficient degree to cause the nerve to be red and congested is associated with blindness, whereas papilledema of the nerve is not. I should say that the two conditions could be differentiated by a test of the visual acuity and examination of the visual fields instead of by the use of the binocular ophthalmoscope.

DR. LEWIS D. STEVENSON: One explanation for the absence of papilledema which may be rare is that a tumor of the posterior fossa occasionally may decompress itself. I am thinking of a case that Dr. Hausman and I described in a man about 51 years of age who had had a huge tumor of the cerebellum for at least forty-five years and was never operated on. This patient had been observed by Drs. Sachs and M. Allen Starr and a number of other eminent neurologists and physicians; the patient never had papilledema. Postmortem examination of the brain disclosed an enormous internal hydrocephalus and tremendous hydrops of the third ventricle. The anterior half of the aqueduct had become so widened that the roof was as thin as tissue paper and was translucent. Our explanation of this man's attacks of headache and vomiting, with remission throughout life, was that the fluid had escaped through the roof of the thinned-out aqueduct into the subarachnoid space. We made some pictures in this case which bore out our explanation as to why the patient did not have choked disk and lived so long. I wish to ask Dr. Cohen if the absence of papilledema in any of his cases could possibly be explained on such a basis.

DR. IRA COHEN: In answer to Dr. Stevenson, I doubt if the explanation would hold in those cases in which recovery occurred; in those in which autopsy was performed it did not hold, because no such condition was found.

In answer to Dr. Kennedy, I do not have the figures on refraction in my cases. As a rule they were not recorded on the chart. The ophthalmologist did not make any note of myopia, and while it is possible that 50 per cent of the patients have had high grade myopia, I think that that is a high proportion. Part of the explanation for the absence of papilledema lies in the fact that all hospitals receive patients earlier than they used to. After I had written this paper I reviewed the records at the hospital rather hurriedly. The system in the record room had been changed,

and there was no routine way to choose the cases. However, I selected 17 which occurred between 1925 and 1930. In that group there were 12 cases of tumor with papilledema and 5 without, as opposed to the present series of cases in which there were 18 with papilledema and 17 without.

THE SENSE OF SMELL: THE VALUE OF QUANTITATIVE OLFACTORY TESTS FOR THE LOCALIZATION OF SUPRATENTORIAL TUMOR OF THE BRAIN; A PRELIMINARY REPORT. DR. CHARLES A. ELSBERG.

My colleagues and I became interested in the subject of olfaction because of a desire to learn whether meningioma of the cribriform plate, which is usually operated on when the growth is large, could be recognized earlier by carefully performed tests of the sense of smell. From the onset such a tumor must press on the olfactory bulb or tract. By testing the sense of smell one should be able to diagnose the condition early. We investigated various olfactory tests but found that none was sufficiently sensitive for the purpose. Unless the sense of smell was lost on one or on both sides, the procedures ordinarily used were found to be of little value. Even if the odors used for the tests were carefully diluted, as was suggested by Proetz, or some type of olfactometer such as that of Zwaardemaker was used, the fact that the odors were inhaled made it impossible to measure the quantity of odor which entered the nasal passages. It was necessary to discover some new method which was both sensitive and quantitative.

A new procedure was devised which was based on a new principle. It is well known that odors cannot be perceived or identified unless they are inhaled into the nasal passages and that no matter how volatile the odorous substance there is no smell without breathing. We found that if an odor is injected it can be recognized even though the subject is holding his breath. This led us to devise a procedure which consists of the injection of odors into the nasal passages during a short period of voluntary cessation of breathing. In this new procedure the force of the injection takes the place of the inspiratory movement. The apparatus required for the tests is simple, and the method is easily learned.

The procedures, which are called "blast injection" and "stream injection," have made it possible to establish numerical values for different odorous substances and for the degree of fatigue produced by different odors. We have been able to gain information concerning the relation between the amount of the olfactory stimulant used and the depth and duration of the resulting fatigue and also to gain some insight into the physiologic significance of olfactory fatigue.

The apparatus consisted of a test bottle of a fixed size for the odorous substances and appropriate nosepieces. A known volume of odor is injected into one or into both nasal passages at a known pressure. The number of cubic centimeters that have to be injected into one nasal passage in order that the odor may be identified by the subject who is being examined is called the minimum identifiable odor (M. I. O.) and the M. I. O. on bisynchronorhinal injection is called the olfactory coefficient of the odorous substance. By this method we have been able to establish numerical values for the acuity of monorhinal and birhinal smell. We have found that the efficiency of the olfactory receptors, although very sensitive to a number of influences, is about the same in all normal persons.

Fatigue of the sense of smell was produced by the injection of odors into one or into both sides of the nose in a continuous stream, and the duration of the ensuing fatigue was found to be proportional to the duration of the stream injection and the volume rate of the stream. By this procedure we were able to compare the duration of monorhinal fatigue with that of birhinal fatigue. When one nosepiece was used for olfactory stimulation and another for testing olfactory acuity, it was possible to study the effect of unilateral stimulation on birhinal smell and, vice versa, the effect of bilateral stimulation on monorhinal smell and the effect of the injection of an odor into one nasal passage on the olfactory acuity of the other side. The conclusion was arrived at that there is a definite influence through neural channels of stimulation of the receptors of one side on the efficiency of those of the other side of the nose.

In order to establish numerical values for the acuity of monorhinal and birhinal smell and for the normal duration of olfactory fatigue produced by different odors, a large number of tests with a variety of odorous substances were made on normal persons. The results of some studies, made with Dr. I. Levy and Dr. E. D. Brewer, have already been published (*Bull. Neurol. Inst. New York* **4**:1-31 and 264-286, 1935); other papers will soon appear. The studies yielded interesting information regarding the effect of odorous substances on the olfactory receptors and the trigeminal nerve, the relative importance of the pressure and the volume of the olfactory stimulant, the physiologic significance of olfactory fatigue and the parts of the brain concerned in this alteration of function. After having investigated the effect of a large number of odorous substances on the olfactory receptors, we selected coffee and citral as best adapted for clinical tests of the sense of smell.

After the basic studies above outlined had been made the tests were used on persons suspected of having tumor of the brain in order to learn whether the procedures were of value for the localization of intracranial growths.

1. The M. I. O. of each side of the nose was determined by unilateral blast injections of the odors of coffee and citral. The normal M. I. O. of the odor of coffee when injected into one nasal passage is usually between 8 and 9 and that of citral between 7 and 8. (Occasionally citral is identified when a smaller quantity [6 or even 5 cc.] is injected. These persons recognize the odor partly from its marked effect on the trigeminal nerve.)

2. Unilateral fatigue was produced by a stream injection of the odor for thirty seconds at a volume rate of 2,000 cc. to the minute. The normal duration of fatigue for coffee produced by this procedure is between one and a half and two and a half minutes, and that for citral, between two and three minutes.

Summary.—1. When a neoplasm exerts pressure on one olfactory bulb or tract, the M. I. O. of that side is higher than normal, and a larger quantity of the odor has to be injected into that side of the nose before the odor can be identified. If both olfactory nerves are involved, the M. I. O. of each side is higher than normal, the greatest increase being found on the most affected side. This diminution in unilateral or bilateral olfactory acuity occurs in association with an expanding lesion on the under-surface of the frontal lobe. It was regularly found in cases of suprasellar meningioma and in cases of aneurysm of the internal carotid artery or the anterior part of the circle of Willis. In cases of adenoma of the pituitary gland in which the growth has not extended beyond the confines of the sella turcica, the M. I. O. is within normal limits, but if the growth projects above the sella turcica the olfactory tracts are subjected to pressure and the M. I. O. of one or of both sides of the nose is higher than normal. In all of these cases the duration of olfactory fatigue was not longer than normal.

2. In cases of intracerebral tumor or of a large dural growth that has become buried in the brain, the M. I. O. is not raised, but the duration of fatigue is prolonged on the same side as that of the neoplasm.

3. In cases of tumor in or near the midline of the cranial cavity, such as a parasagittal meningioma or an infiltrating growth which extends to the mesial surface of one cerebral hemisphere, and in cases of tumor of the corpus callosum or of some other midline growth, the duration of fatigue produced by the stream injection of odors is prolonged and lasts for more than ten minutes.

4. In cases of tumor of the frontal lobe in which the growth extends to the under-surface of one lobe so that the olfactory bulb or tract is subjected to direct pressure, the M. I. O. on the affected side is higher than normal and the duration of fatigue is prolonged.

5. In cases in which there is a generalized increase of intracranial pressure there is often an increase in irritability of the olfactory pathways so that the M. I. O. is lower than normal.

The possibilities of the tests are by no means exhausted when the procedures described in this paper have been used. The investigations of the effect of fatigue

on one side of the nose on birhinal smell and of bilateral fatigue on monorhinal smell in patients with a tumor of the brain may make it possible to localize the growth more exactly. Furthermore, the study of the effect of odors on the trigeminal nerve may be of value for the localization of a tumor in the posterior cranial fossa and the differentiation between a growth in a cerebellar hemisphere and one in a lateral recess. We have already made a few tests on patients with lesions in the posterior fossa which point in that direction. When there is a question whether the neoplasm is in the posterior fossa or in or underneath the frontal lobe, the occurrence of an abnormally high M. I. O. will indicate that the neoplasm is not cerebellar. The tests should therefore be of value for the differentiation between growths in these two situations. Our investigations of the value of the olfactory tests for the localization of a subtentorial growth are still so limited that a report on the subject must await more extensive observations.

In a few patients with papilledema in whom a tumor was suspected, the olfactory tests showed that the duration of fatigue was normal on each side of the nose, while the M. I. O. was abnormally low, and later encephalography or ventriculography demonstrated that the ventricles were normal in size, shape and position, the subarachnoid cisterns were not deformed and the sulci were normal in position. Therefore, it is not beyond the range of possibility that the olfactory tests may have some value for diagnosis as well as for localization.

Until the tests have been made in a large number of cases, it is advisable to be conservative in the conclusions drawn from the use of a new diagnostic procedure. However, the experiences recounted in this paper show that information of value may be gained by the use of these new fine quantitative tests of the sense of smell.

DISCUSSION

DR. FREDERICK TILNEY: I think that one can truly say that this is a neurologic occasion. A real contribution, based on clinical research, has been presented. It has been my privilege for the last number of years to be Dr. Elsberg's next door neighbor. The door between our offices has been open, so that I have had access and been able to watch him as he has been carrying on this beautiful piece of work. With remarkable simplicity of method and yet with great ingenuity and wonderful scholarly insight he has carried on an investigation which is revealing not merely in the clinical field but also in the fields of physiology and physics. I suppose that he felt that he did not have time to tell all the things he has done in this investigation. So I may in the discussion say something about this important addition to his work. Heretofore, olfactory substances have been roughly and crudely classified. Now as a result of this work they are scientifically classified, because Dr. Elsberg has proved that the olfactory coefficients of all odor-bearing substances vary directly as their boiling points. Naturally I am impressed by certain physiologic and structural implications in his work; the first thing that impresses me is that the "smell brain," that is, the part of the brain which is used for that particular function, is much more extensive than has heretofore been thought, and probably much more sensitive, or it may be both of these. For example, he has shown that pressure on known portions of the smell brain produces definite blocking and that more remote disturbances which are known to be olfactory in nature also give rise to an alteration in the sense of smell. One alleged part of this olfactory or smell brain is the hippocampus (the archicortex), and there is reason to believe that the function of that part of the brain is not confined to the olfactory sense alone. Another part is the paleocortex, and there is ample reason to believe that this part of the brain has had somatic function, if it does not have it at the present time, so that what has been thought of as the rhinencephalon and what has been taught to be the rhinencephalon, to the everlasting confusion of the student mind, probably does not exist. There is a much more diffuse representation of the sense of smell in the brain than is ordinarily recognized. One has a right to say that the new part of the brain, the neocortex, also plays an important part in the sense of smell, in addition to the ancient parts that are known to be connected with it in some way. Otherwise, how is it that so much social adjustment

is based around the sense of smell, so much esthetic appreciation and so much highly commercialized exploitation?

Perhaps the members remember a letter that Helen Keller wrote me a number of years ago describing her sense of smell, which is nearly intact. She said that it was her center, the background of her life, and that most of the things that she did had this particular sense as their basis. She wrote in that letter a quotation from Pierre Loti and also quoted from memory and in full Shakespeare's ninety-ninth sonnet. I believe that when the sense of smell can reach that degree of elaboration it is difficult to believe that the neocortex is not involved in it.

There is another point of much interest to me in Dr. Elsberg's work, namely, his rather significant suggestion about the corpus callosum. He thinks, and I believe rightly, that this part of the brain is connected with the sense of smell. The corpus callosum begins (and one must remember that the olfactory sense is the most primitive of the special senses) far forward, in the region connected with the olfactory cells. He also, although he did not mention it tonight, spoke about the anterior commissure, which he thinks is a chiasm, like the optic chiasm. I should like to believe that too, but at the present time my evidence is not sufficient. I am inclined to think that the anterior commissure is connected with the sense of smell in a commissural rather than in a chiasmal manner.

Last Sunday I had the privilege of visiting what is perhaps the most famous private laboratory in the world. For the last two years the Berger rhythms of the brain have been the subject of study. The results are remarkable. I should like to point out that this work has been carried out on human beings. The record of a patient asleep in a room about 200 feet away shows what is called the 10 cycle rhythm of normal consciousness. The moment the patient awakes or is awakened these waves disappear. In this laboratory they have taken the position, and I think rightly so, that the most important researches that can be made in the investigation of the nervous system are those which can be made on man. After all, the clinical investigator is the court of last appeal. The guinea-pig and the Macacus rhesus, and even the higher apes, have been overglorified. What one must have is the test of facts on human beings, and I think in that respect Dr. Elsberg has taught a great lesson in dealing with this sense, which I call the "forgotten sense" because in all the case histories that I read at the Neurological Institute there were few statements about the sense of smell. Yet how important this sense may be clinically! This afternoon I was talking with Dr. Elsberg, and he told me that he saw a patient this morning who he knew had a meningioma—not a deep, penetrating one—attached to the sphenoid ridge on the left side. All he had done in coming to that conclusion was to carry out these tests for the sense of smell. He had made no roentgenograms and had no other means of testing to help him in forming this opinion. If the neurologists can learn from a master such as he the technic of sensory examinations—not merely for the sense of smell but for all the other senses—they will cease to be the slaves of the laboratory and will become once more masters of clinical neurology.

DR. FOSTER KENNEDY: Nothing remains for me but to endorse what Dr. Tilney has said concerning Dr. Elsberg's paper. He has taught clinicians a real lesson—to turn for knowledge to the patient. He has done that in a simple and direct manner, and he has been aware of a fact which I am sometimes fond of illustrating by telling a story about Peter, who saw a great sheet let down from Heaven full of all manner of creeping and crawling things. Starting back from this horrid thing, he heard the voice of God from on high saying, "Call nothing that I have created common or unclean." Dr. Tilney has said that the sense of smell is a forgotten sense, and Dr. Elsberg has had the imagination—for that is what started him—to go to a forgotten sense, to a sense that is little described clinically and seemingly of no great moment. By meticulous attention, precision and great perseverance he has discovered some interesting facts. I feel myself lacking in qualities that I think Dr. Elsberg has exhibited, because at one time in my life I was much interested, as some of you may know, in the symptomatology of tumors beneath the frontal lobe. I put together a kind of diagnostic syndrome

which has been of a little value, but my attention was caught, in vulgar fashion, by the more obvious facts regarding the effects of pressure on the optic nerve in that area. True, I did describe reduction in olfaction on the side of the neoplasm, but my ideas regarding that were empty and vacuous, and my clinical research in the sense of smell was far away from the precision of detail that Dr. Elsberg has mastered.

Dr. Tilney speaks of memory as being in touch with the neocortex, and perhaps it is a link between the old and the new. Oliver Wendell Holmes developed a great deal of discussion in, I think, "The Professor at the Breakfast Table," on the philosophic idea of why, of all the senses (and I think this obtains for the majority of mankind), smell should be the most potent stimulus for the evocation of an ancient memory. My notion that the engrams of the far-distant memories of one's life may be written by molecular arrangement in the temporosphenoid lobes may be familiar to some, and I have thought that there was biologic reason, which I shall not go into now for this idea. But perhaps the relation in locale between such a reservoir of old memory in the temporal lobes and the adjacent connecting hippocampal lobes may have something to do with the psychologic association of olfaction and memory.

To return for a moment to the conclusion of Dr. Elsberg's address, I am sure that Dr. Elsberg would be the first to want to establish in his material the normality of the mucous membrane. The normality of the receiving apparatus must, of course, be carefully determined, and it is known from day to day experiences how sensitive is the mucous membrane of the nose in its ability to take up impressions and how frustrated and deteriorated it can be by a small local infection. Dr. Elsberg spoke of enlarged turbinates and disturbed septums as being capable of changing the acuity of olfaction, but in any given case in which one wishes to use this method as a highly important diagnostic contribution one must have the ability to establish the normality of the peripheral olfactory apparatus.

When I was interested at one time in the syndrome of lesions of the temporal lobe I became aware that a central unilateral lesion of the temporal lobe (without having used Dr. Elsberg's method of precision) fails to reduce ipsilateral olfaction; there was a bilaterality of representation of smell whereby no obvious reduction in smell was caused by a hippocampal central lesion on one side. However, one knows that sometimes a complete and often permanent abolition of taste and smell can come about by the common cause of fracture across the middle fossa. I have seen at least twenty such cases in which the patient had suffered a loss of taste and smell from a bilateral lesion of the middle fossa. But I have noted no such results from a unilateral lesion, and I should like to ask Dr. Elsberg if he has made any research with his method in such cases.

I was much impressed by Dr. Elsberg's ability to note the progress of a tumor of the pituitary gland out of the sella turcica by reason of a change in olfaction on one side. This is a contribution to the diagnostic armamentarium of great significance. Dr. Elsberg did not say, or at least I am not sure that he said, whether the condition in these cases was verified by postmortem examination or by operation or whether it was diagnosed only clinically.

Dr. Charles Elsberg: In every case to which I referred the diagnosis was verified. All cases in which verification was not made have been excluded.

Dr. Foster Kennedy: I am glad I brought up the point of verification as it may not have been clear to some of the members and it has enormously increased the accuracy of these experiments. I am happy indeed to see a man of such eminence as Dr. Elsberg refuting the equation which has obtained so long in medical education and medical research, that is, that it takes observations on 10 men to equal those on 1 guinea-pig!

Dr. George V. N. Dearborn: Every descriptive and many experimental psychologists will welcome this new method. The subject of odors has been a vague one and a bête noir of the science from the beginning of psychology up to the present time. This method will also be useful in studying the phenomena of fatigue.

I want to ask Dr. Elsberg whether he has any data on taste in the course of this work. If I remember my physiology of an earlier year correctly, there used to be a "few taste buds scattered through the Schneiderian membrane."

DR. J. H. LEINER: I should like to ask Dr. Elsberg if he used percentage bases for his test solutions to determine the acuity of the sense of smell. I ask this because I pursued such an investigation at the Montefiore Hospital about twelve years ago, using the sniffing method and the modified Zwaardemaker approach. I can appreciate the difficulty of Dr. Elsberg's work, because at that time I tried to standardize test solutions on a percentage basis, using the oil of rose and the oil of cinnamon as solutions for testing the acuity of the sense of smell. When I reached dilutions of 1:50,000 the person would smell the diluents of olive oil or liquid petrolatum and not the oil of rose or the oil of cinnamon. I also found similar results in the matter of fatigue. I used members of the staff and a number of other persons to reach a basis for the norm. For instance, if I used oil of cinnamon in a dilution of 1:10,000 they would keep on retaining the odor of cinnamon for a considerable length of time, and then I would be compelled to use much stronger solutions to induce smell for other odors. Another thing I found was that I could detect persons whose olfactory system was probably affected (without local defects) by excessive tobacco smoking. These were the heavy smokers. They would show a loss of acuity of the sense of smell in the higher levels.

My problem was not a surgical one but one in testing the sense of smell in persons with neurosyphilis. I asked myself why in persons with tabes there was so often atrophy of the second cranial nerve and not the olfactory system, which is a more primitive cerebral mechanism. I tried to find the acuity level of the norm, and this led me to investigate the sense of smell.

DR. CAESAR HIRSCH: In the paper which I read before this society several months ago (Ueber die klinische Prüfung des Geruchs- und Geschmacksinnes, *München. med. Wchnschr.* **79**:1234 [July 29] 1932) mention was made of a method first described by Boernstein (Ueber den Geruchssin, *Deutsche Ztschr. f. Nervenh.* **104**: 55, 1928), a former co-worker of Kurt Goldstein. My colleagues and I had excellent results with it, especially in differentiating malingerers and those with organic lesions. Physiologists have given a number of methods to test the sense of smell (Zwaardemaker, Hofmann, Kohlrausch and Skramlik). A former co-worker of mine, Dr. Teufer, has devised another method (*Verhandl. d. Gesellsch. d. deutsch. Hals-, Nasen- und Ohrenaerzte,* 1925) similar to, but not as elaborate as this one.

DR. CHARLES ELSBERG: Man as compared to animal has been called microsmatic, but the more one investigates the sense of smell in human beings, the more one becomes convinced that such a distinction is not justified. In man the sense of smell is very sensitive and easily influenced by slight factors. How sensitive the olfactory sense is can be shown by a simple experiment: If the M. I. O. for oil of peppermint is established and the person tested then chews a piece of peppermint candy for a few minutes, the M. I. O. for peppermint will be found to be considerably higher after the candy has been chewed than it was before. Ordinary colds in the head produce profound changes in the sense of smell. After an attack of acute rhinitis a person may lose the sense of smell for a day or two, after which it apparently returns to normal. If such a person is examined by the blast injection procedure, the M. I. O. will be found to be much higher than normal, and from six to twelve weeks will elapse before it returns to normal. This shows that the disturbance of the olfactory mucous membrane from an ordinary cold is really profound.

Dr. Kennedy has raised the question of the significance of infections of the nasal mucous membrane. Before making the olfactory tests one must always inquire whether the patient has recently had a cold in the head, and the Zwaardemaker exhalation test must always be made. If there is no previous disease of the nasal mucous membrane, such as ozena, and if the patient has not recently had

acute rhinitis, the nasal passages will be found to be equal in size by the Zwaardemaker test, and under these conditions normal responses will be obtained by blast injection tests.

Up to the present time we have limited our investigations to persons with tumor of the brain, primarily because of interest in intracranial expanding lesions. The tests on the patients were made by Dr. Levy, Dr. Brewer and me on patients in whom tumor of the brain was suspected, and some patients were found not to have a neoplasm. In the future the tests will be made on patients with different types of intracranial disease.

We have not investigated the sense of taste. It is my belief that the methods used at present for the examination of the sense of taste are very crude, and real quantitative methods for testing the gustatory sense must be devised.

Dr. Leiner has asked regarding the strength of solutions we use. For coffee we used pure ground coffee, and the citral was the chemically pure oil of lemon. In our investigations we used a large number of odorous substances, but we found that the results of the tests were not as exact as when chemically pure odorous substances were used.

As regards the effect of tobacco, we have found that as far as the blast and stream injection tests are concerned, there are no differences between smokers and nonsmokers. It may be that the smoker has not as acute a sense of smell when the odors are drawn into the nose, because inhalation of tobacco smoke may cause swelling of the mucous membrane of the nose, but when the tests we have described are used the odor is injected in the optimum direction to the olfactory cells, and the slight alteration in the nasal passages due to a slight swelling of the mucous membrane makes no difference.

This is a preliminary report, and it is always wise to be conservative when describing results obtained by a new procedure. However, the information gained by these tests appears to be reliable, and the results in patients have been almost disconcertingly constant. The tests have given us considerable information regarding the physiology of smell and the anatomic areas of the brain concerned in smell. I believe that the anterior commissure is really a chiasm and that the summation of smell occurs either through the anterior or through the hippocampal commissure. Fatigue of the sense of smell is not due to fatiguing of the olfactory receptors or of the nerves, bulbs or tracts but is due to a change in the brain itself. It would take more time than has been allotted to me if I were to explain the reasons that led to these conclusions. Further investigations should give much more knowledge concerning the areas in the brain which have to do with olfaction and the relative importance of each, and in the future it should be possible to localize a tumor of the brain much more exactly with tests of olfactory acuity.

The production of fatigue by stream injection requires an apparatus which is a little more complicated, because a tank of compressed air is necessary. For a number of months we have been studying the fatigue produced by frequently repeated blast injections, and I think that in the near future it will be possible to produce fatigue by means of blast injections. When this has been accomplished, all the tests can be made with two test bottles, nose-pieces, a syringe and a stop-watch.

Book Reviews

Basic Problems of Criminology. By Prof. Olof Kinberg, M.D., University of Stockholm. Paper. Price, 20 kroner. Pp. 436. Copenhagen, Denmark: Levin & Munksgaard, 1935.

Kinberg states at the outset that this book is the result of an investigation into possible means of preventing the punishment of insane persons. It is an attempt to uproot "medieval prejudices" on crime and punishment. It is therefore written with the chief emphasis on the study and understanding of the individual criminal from a psychiatric, medical and sociologic point of view.

The author discusses the question of moral responsibility, which forms the basis on which the sociolegal treatment of the problem depends, and states that the concept of "freedom of the will" is untenable. He points out that this concept is chiefly responsible for the failure of the sociolegal treatment of crime to keep pace with progress and development in other sciences. In some countries of Europe and in some states of the United States an attempt has been made to arrive at a practical solution of the problem of "imputability" by substituting the positivist concept of "dangerousness." This has led directly to the adoption of the indeterminate sentence, together with a shifting of emphasis from punishment to the treatment of criminals and to segregation as a practical means of protection to society.

In chapters on the causes of crime Kinberg presents an excellent discussion of environmental and individual factors. He makes his position clear in respect to the relative importance of the two factors, namely, that in common with European criminologists he tends to lay chief emphasis on the endogenous factors in criminality, while North American criminologists emphasize the exogenous, or social, factors. He states: "A fact of great importance is the apparently slight influence exercised by the penal laws [in North America] on the public opinion on morals. The legislative mill grinds as it does in European countries, but the average American cares little what comes out of it." Again, "A point of great importance is that crime in America is so lucrative a profession." He warns that great caution must be exercised in any comparison of European and American research because of the widely differing social conditions.

Consistent with his approach to the subject, Kinberg discusses in considerable detail, well illustrated by cases, the various factors in crime. He emphasizes particularly morphologic types, endocrinopathies and hereditary factors, citing statistics from studies made by other authors, most of whom are European. The same objection to the use of such statistical material holds true in this study as it does in all attempts to correlate morphologic structure with some more or less specific type of human behavior, namely, that the correlations arrived at from such data cannot be considered conclusive until control studies are made on the general population. The value and importance of the material per se to the whole field of criminology is, of course, not questioned, and it is this aspect which the author emphasizes.

Because the courts so frequently fail to recognize mental and physical states which should affect the judicial disposition in a given case, Kinberg advocates medical and psychiatric examination of every accused person before judicial action is taken. He advocates further that all officials connected with the courts undergo a course in criminologic training. He refers to the criminologic diagnostic clinics of the states of New York and Illinois as examples of progress in the study and treatment of convicted criminals.

In his discussion of general prophylactic measures against crime, Kinberg emphasizes the importance of child guidance clinics and makes an especially strong plea for legalizing eugenic control of mentally and physically defective members of society.

Malarial Therapy of Neurosyphilis and Other Diseases of the Nervous System. By P. A. Miniovich. Second, enlarged edition. Price, 8 roubles. Pp. 229. Rostov-on-the-Don, U. S. S. R.: Azov-Chernomorsk Regional Publishing Company, 1935.

This monograph embodies the author's experience with some 1,100 cases of various forms of syphilis of the central nervous system, treated by malaria in the Neurology Clinic of the Rostov University. Miniovich shows an extensive knowledge of the foreign literature and constantly compares his results and ideas with those expressed elsewhere, so that one gets a full exposition of the subject.

Both tertian and quartan malaria were used in the treatment. Among 220 cases of dementia paralytica complete remissions occurred in 21.8 per cent, incomplete remissions in 24.1 per cent and improvement in 22.3 per cent. There was no change in 28.1 per cent, and death occurred in 0.3 per cent. Miniovich explains that his unusually favorable results are due to the fact that in the patients treated the disease was fairly acute and recent.

Miniovich is in favor of a second course of malarial therapy but recommends a different type of malaria. Thus, if the first course was given with tertian malaria he would use quartan for the second course. He has found that other types of fever therapy are less effective than malarial therapy.

Among 260 cases of tabes there was improvement in 86.3 per cent, if one uses as a criterion the disappearance of shooting pains. In only a few cases was there improvement in gastric crises.

Malarial therapy was also used in 127 cases of meningovascular syphilis. The best results were obtained in the acute meningitic forms. Definite improvement took place in 46 of 62 cases. The improvement manifested itself in modification of the serologic reaction and in disappearance of annoying paresthesias, headaches, irritability, dizziness and paralyses of individual nerves. In all such cases intense chemotherapy should follow treatment with malaria. The author discusses the question of the prevention of involvement of the central nervous system by prophylactic inoculation with malaria. He expresses a rather conservative point of view and states the belief that there are not sufficient data to warrant conclusions. He is optimistic about the treatment of congenital syphilis, having noted improvement in 14 of 27 cases.

In the later chapter Miniovich discusses his experience with other diseases of the nervous system, such as epilepsy and schizophrenia. He found that improvement is shown only in those cases of epilepsy in which syphilis plays a rôle. In regard to schizophrenia he cites his experience with 108 cases. In cases in which the condition was chronic he observed frequent remissions, which lasted only from one to three months. In cases in which the condition was acute he found marked improvement in 6 of 9 cases, with social recovery of the patients.

On the whole, this is a comprehensive, well documented and thoughtful piece of work. It is unfortunate that similar monographs on treatment with malaria of various diseases of the central nervous system are not available in the English language.

Nouveau traité de psychologie: IV. Les fonctions et les lois générales. By Georges Dumas. Price, 120 francs. Pp. 528. Paris: Félix Alcan, 1934.

In this fourth volume of the series under the editorship of Georges Dumas the general functions of psychologic organization are reviewed by such able authorities as Piéron, Delacroix and Dumas himself. The chapters on attention and on memory and learning, written by Piéron, are concise and well documented surveys. They take no account, however, of the work of the *Gestalt* school, an omission which will seem surprising to the American reader, who has found this work important in the fields of memory and learning as well as in the field of perception. Delacroix' brief chapter on the association of ideas follows the two chapters by Piéron, and fits in well with these in point of view. Neither author accepts the

associationist doctrine in its old rigidity, but both would agree that the relations constituting mental life are to be found in the classic laws of association.

This survey of the organization of mental activity is continued by a long and rather discursive chapter on "schematization" by d'Allonnes, who attempts to replace static conceptions of mental activity in terms of images and ideas by dynamic conceptions but makes no new contributions which add to the vigor of the dynamic view. Dumas' chapter on symbolism, similarly, is not new, but it is an extremely interesting and well written account of symbolism in language, emotional expression and literature.

Part I of this volume of the "Nouveau traité" will be of interest chiefly to the psychologist; Part II, on the general laws of mental activity, will be of interest to the neurologist and to the psychiatrist. Blondel contributes to this section a chapter on automatic and synthetic activity; here he discusses critically the significance of the term "automatic" and the impossibility of considering automatic activity in the psychologic sense as strictly mechanical. He includes a discussion of the two conceptions of the factor of automatism in mental disorders: the idea of a defect in synthesis and control, which permits normal automatisms to play an abnormal part, and the idea that the disorder reflects not simply a defect of control but a new element, with automatic activity which is in itself abnormal.

In the second chapter Janet briefly summarizes his well known theory of psychic tension and discusses the oscillations of psychic tension in sleep, fatigue, emotion and mental disorders. In the third chapter Poyer reviews the topics of mental work and fatigue, and in the fourth Claparède discusses sleep. The last two chapters, like the first two by Piéron, contain surveys of a great deal of experimental material.

For general usefulness to the reader this volume has the advantage of including a bibliography for each chapter but the disadvantage of including no index. The chief value of the book in this country, however, lies probably not so much in its merits as a reference work as in the fact that it represents the point of view of French psychology on important problems of mental organization.

Prostitution: An Investigation of Its Causes, Especially with Regard to Hereditary Factors. By Tage Kemp. Paper. Price, $10. Pp. 253. Copenhagen: Levin & Munksgaard, 1936.

Kemp has studied medically and psychiatrically five hundred and thirty prostitutes in Copenhagen during the years 1931 to 1935. About 45 per cent were slightly or definitely retarded intellectually; 7 per cent were slightly feebleminded; 22 per cent were classified as suffering from psychopathy and 8 per cent as suffering from some other mental disease. Alcoholism, criminality, suicide, oligophrenia, psychopathy or some other mental disease was a feature in the history of at least one relative of 65 per cent of the prostitutes. The importance of these features as hereditary factors is questionable. The early environment of the subjects was found to be poor in two thirds of the cases. A variety of conditions are said to have precipitated the adoption of the rôle of a prostitute, such as unfavorable influence by other members of the family or by pimps, bad working conditions and poverty.

Kemp concludes that imprisonment and fines are ineffective in changing the woman's mode of life; he stresses the importance of mental hygiene studies and advocates improvement in working conditions. An interesting chart is given to show a correlation between the frequency of prostitution and unemployment.

It is doubtful whether this report adds much to the understanding of prostitution. Although the frequency of inadequacies of personality in prostitutes is emphasized, the estimate of these inadequacies is based on only one or two interviews with each subject, together with histories which are admittedly incomplete and unreliable.